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HCV-Related Mortality Among HIV/HCV Co-infected Patients: The Importance of Behaviors in the HCV Cure Era (ANRS CO13 HEPAVIH Cohort)

Melina Erica Santos, Camelia Protopopescu, Philippe Sogni, Issifou Yaya, Lionel Piroth, François Bailly, Fabienne Marcellin, Laure Esterle, Linda Wittkop, Eric Rosenthal, et al.

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AIDS and Behavior

HCV-Related Mortality Among HIV/HCV Co-infected Patients: The Importance of Behaviors in the HCV Cure Era (ANRS CO13 HEPAVIH Cohort)

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Corresponding Author:	Maria Patrizia Carrieri, PhD SESSTIM UMR 1252 Marseille, FRANCE	
Corresponding Author Secondary Information:		
Corresponding Author's Institution:	SESSTIM UMR 1252	
Corresponding Author's Secondary Institution:		
First Author:	Melina Erica Santos, MD, MPH, PhD candidate	
First Author Secondary Information:		
Order of Authors:	Melina Erica Santos, MD, MPH, PhD candidate	
	Camelia Protopopescu, PhD	
	Philippe Sogni, MD, PhD	
	Issifou Yaya, PhD	
	Lionel Piroth, MD, PhD	
	François Bailly, MD	
	Fabienne Marcellin, PhD	
	Laure Esterle, PhD	
	Linda Wittkop, MD, PhD	
	Eric Rosenthal, MD, PhD	
	Philippe Morlat, MD	
	Perrine Roux, PhD	
	Wildo Navegantes de Araújo, PhD	
	Dominique Salmon-Ceron, MD, PhD	
	Maria Patrizia Carrieri, PhD	
Order of Authors Secondary Information:		
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Abstract:	Mortality among individuals co-infected with HIV and hepatitis C virus (HCV) is relatively high. We evaluated the association between psychoactive substance use and both HCV and non-HCV mortality in HIV/HCV co-infected patients in France, using Fine & Gray's competing-risk model adjusted for socio-demographic, clinical predictors and confounding factors, while accounting for competing causes of death. Over a 5-year median follow-up period, 77 deaths occurred among 1,028 patients. Regular/daily cannabis use, elevated coffee intake, and not currently smoking were independently associated with reduced HCV-mortality (adjusted sub-hazard ratio [95%CI]: 0.28[0.10-	

	<p>0·83], 0·38[0·15-0·95], and 0·28[0·10-0·79], respectively). Obesity and severe thinness were associated with increased HCV-mortality (2·44[1·00-5·93] and 7·25[2·22-23·6] versus normal weight, respectively). Regular binge drinking was associated with increased non-HCV-mortality (2·19[1·10-4·37]). Further research is needed to understand the causal mechanisms involved. People living with HIV/HCV co-infection should be referred for tobacco, alcohol and weight control interventions and potential benefits of cannabis-based therapies investigated.</p>
Response to Reviewers:	<p>Thank you very much for your comments and important contributions to our work. We hope that after these minor revisions, our manuscript will be suitable for publication in AIDS and Behavior.</p>

Title

HCV-Related Mortality Among HIV/HCV Co-infected Patients: The Importance of Behaviors in the HCV Cure Era (ANRS CO13 HEPAVIH Cohort)

Authors' names

Melina Erica SANTOS^{1,2,3}, Camelia PROTOPOPESCU^{2,3}, Philippe SOGNI^{4,5,6}, Issifou YAYA^{2,3}, Lionel PIROTH^{7,8}, François BAILLY^{9,10}, Fabienne MARCELLIN^{2,3}, Laure ESTERLE¹¹, Linda WITTKOP^{11,12}, Eric ROSENTHAL^{13,14}, Philippe MORLAT¹⁵, Perrine ROUX^{2,3}, Wildo Navegantes de ARAUJO¹⁶, Dominique SALMON-CERON^{6,17}, Maria Patrizia CARRIERI^{2,3} & the ANRS CO13 HEPAVIH Study Group

Authors' affiliations

¹Faculdade de Ciências da Saúde, Universidade de Brasília, Brasília, Brasil.

²INSERM, IRD, SESSTIM, Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale, Aix Marseille Université, Marseille, France.

³Observatoire régional de la santé Provence-Alpes-Côte d'Azur, ORS PACA, Marseille, France.

⁴Service d'Hépatologie, Hôpital Cochin, AP-HP, Paris, France.

⁵INSERM U-1223, Institut Pasteur, Paris, France.

⁶Université Paris Descartes - Sorbonne Paris Cité, Paris, France.

⁷Département d'Infectiologie, CHU de Dijon, Dijon, France.

⁸INSERM - CIC 1342, Université de Bourgogne, Dijon, France.

⁹Service d'Hépatologie et Gastroentérologie, Hôpital de la Croix-Rousse, Lyon, France.

¹⁰INSERM U1052, Centre de Recherche en Cancérologie de Lyon, Lyon, France.

¹¹Bordeaux Population Health Research Center, INSERM U1219, CIC-EC 1401, Univ. Bordeaux
- ISPED, Bordeaux, France.

¹²Service d'information médicale, CHU de Bordeaux, Bordeaux, France.

¹³Service de Médecine Interne, Hôpital l'Archet, CHU de Nice, Nice, France.

¹⁴LAMHESS, Université de Nice-Sophia Antipolis, Nice, France.

¹⁵Service de Médecine Interne et Maladies Infectieuses, CHU de Bordeaux, Bordeaux, France.

¹⁶Faculdade UnB Ceilândia, Universidade de Brasília, Brasília, Brasil.

¹⁷Service de Maladies Infectieuses et Tropicales, Hôpital Cochin, AP-HP, Paris, France.

Corresponding author

Name: Maria Patrizia Carrieri

Mailing address: INSERM UMR1252 SESSTIM. IHU Méditerranée Infection. 19-21 Boulevard
Jean Moulin, 13005 Marseille, France.

Email address: pmcarrieri@aol.com

Telephone number: + 33 04 13 73 22 81

Running head

Behavioral correlates of HCV mortality

Authors' contributions

Study concept and design: MPC, CP, DSC. Acquisition of data: LW, LE, LP, FB, ER, PM, PS, DSC. Analysis and interpretation of data: CP, MES, MPC. Drafting of the manuscript: MES, MPC, CP, FM. Critical revision of the manuscript for important intellectual content: MPC, FM, DSC, WNA, LW, LE, ER, PS, PM, IY, PR, LP, FB. Statistical analysis: CP. Obtained funding: LW, MPC. Administrative, technical, or material support: FM, LE. Study supervision: MPC. All authors approved the final revised version of the manuscript.

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; Virologie : Y. Baazia) ; Hôpital Joseph Ducuing, Toulouse (Médecine Interne : M. Uzan, A. Bicart-See, D. Garipuy, M.J. Ferro-Collados ; Anatomopathologie : J. Selves ; Virologie : F. Nicot) ; APHP Bichat – Claude-Bernard, Paris (Maladies Infectieuses : A. Gervais, Y. Yazdanpanah; Anatomopathologie : H. Adle-Biasette ; Virologie : G. Alexandre) ; APHP Saint-Louis, Paris (Maladies infectieuses : C. Lascoux-Combe, J.M. Molina,; Anatomopathologie : P. Bertheau,; Virologie :M.L. Chaix, C. Delaugerre, S. Maylin) ; APHP Saint-Antoine (Maladies Infectieuses et Tropicales : K. Lacombe, J. Bottero; J. Krause P.M. Girard, Anatomopathologie : D. Wendum, P. Cervera, J. Adam ; Virologie : C. Viala) ; APHP Bicêtre, Paris (Médecine Interne : C. Goujard, Y. Quertainmont, E. Teicher; Virologie : C. Pallier ; Maladies Infectieuses : D. Vittecoq) ; APHP Necker, Paris (Maladies Infectieuses et Tropicales : O. Lortholary, C. Duvivier, C. Rouzaud, J. Lourenco, F. Touam, C. Louisin : Virologie : V. Avettand-Fenoel, A. Mélard) ; CHU Pellegrin, Bordeaux (Maladies Infectieuses et Tropicales : D. Neau, A. Ochoa, E. Blanchard, S. Castet-Lafarie, C. Cazanave, D. Malvy, M. Dupon, H. Dutronc, F. Dauchy, L. Lacaze-Buzy ; Anatomopathologie : P. Bioulac-Sage ; Virologie : P. Trimoulet, S. Reigadas) ; Hôpital Saint-André, Bordeaux (Médecine Interne et Maladies Infectieuses : Médecine Interne et Maladies Infectieuses : P. Morlat, D. Lacoste, F. Bonnet, N. Bernard, M. Hessamfar, J. F. Paccalin, C. Martell, M. C. Pertusa, M. Vandenhende, P. Mercier, D. Malvy, T. Pistone, M.C. Receveur, M. Méchain, P. Duffau, C Rivoisy, I. Faure, S. Caldato ; Anatomopathologie : P. Bioulac-Sage ; Virologie : P. Trimoulet, S. Reigadas) ; Hôpital du Haut-Levêque, Bordeaux (Médecine Interne : J.L. Pellegrin, J.F. Viallard, E. Lazzaro, C. Greib ; Anatomopathologie : P. Bioulac-Sage ; Virologie : P. Trimoulet, S. Reigadas) ; Hôpital FOCH, Suresnes (Médecine Interne : D. Zucman, C. Majerholc ; Virologie : E. Farfour) ; APHP Antoine Bécclère, Clamart (Médecine Interne : F. Boué, J. Polo Devoto, I. Kansau, V. Chambrin, C. Pignon, L. Berroukeche, R. Fior, V. Martinez ; Virologie : C. Deback) ; CHU Henri Mondor, Créteil (Immunologie Clinique : Y. Lévy, S.

Dominguez, J.D. Lelièvre, A.S. Lascaux, G. Melica) ; CHU Hôtel Dieu, Nantes (Maladies Infectieuses et Tropicales : E. Billaud, F. Raffi, C. Allavena , V. Reliquet, D. Boutoille, C. Biron; Virologie : A. Rodallec, L. Le Guen) ; Hôpital de la Croix Rouse, Lyon (Maladies Infectieuses et Tropicales : P. Mialhes, D. Peyramond, C. Chidiac, F. Ader, F. Biron, A. Boibieux, L. Cotte, T. Ferry, T. Perpoint, J. Koffi, F. Zoulim, F. Bailly, P. Lack, M. Maynard, S. Radenne, M. Amiri ; Virologie : C. Scholtes, T.T. Le-Thi) ; CHU Dijon, Dijon (Département d'infectiologie :, L. Piroth, P. Chavanet M. Duong Van Huyen, M. Buisson, A. Waldner-Combernoux, S. Mahy, R. Binois, A.L. Simonet-Lann, D. Croisier-Bertin) ; CH Perpignan, Perpignan (Maladies infectieuses et tropicales : H. Aumaître) ; CHU Robert Debré, Reims (Médecine interne, maladies infectieuses et immunologie clinique : F. Bani-Sadr, D. Lambert, Y Nguyen, J.L. Berger) ; CHRU Strasbourg (Le Trait d'Union : D Rey, M Partisani, ML Batard, C Cheneau, M Priester, C Bernard-Henry, E de Mautort, Virologie : P Gantner et S Fafi-Kremer), APHP Bichat-Claude Bernard (Pharmacologie : G. Peytavin). Data collection: F. Roustant, I. Kmiec, L. Traore, S. Lepuil, S. Parlier, V. Sicart-Payssan, E. Bedel, F. Touam, C. Louisin, M. Mole, C. Bolliot, M. Mebarki, A. Adda-Lievin, F.Z. Makhoukhi, O. Braik, R. Bayoud, M.P. Pietri, V. Le Baut, D. Bornarel, C. Chesnel, D. Beniken, M. Pauchard, S. Akel, S. Caldato, C. Lions, L. Chalal, Z. Julia, H. Hue, A. Soria, M. Cavellec, S. Breau, A. Joulie, P. Fisher, C. Ondo Eyene, S. Ogoudjobi, C. Brochier, V. Thoirain-Galvan. Management, statistical analyses: E. Boerg, P. Carrieri, V. Conte, L. Dequae-Merchadou, M. Desvallees, N. Douiri, L. Esterle, C. Gilbert, S. Gillet, R. Knight, F. Marcellin, L. Michel, M. Mora, C. Protopopescu, P. Roux, B. Spire, S. Tezkratt, I. Yaya, T. Barré, T. Rojas, V. Villes, M. Baudoin, M. Santos.

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Mortality among individuals co-infected with HIV and hepatitis C virus (HCV) is relatively high. We evaluated the association between psychoactive substance use and both HCV and non-HCV mortality in HIV/HCV co-infected patients in France, using Fine & Gray's competing-risk model adjusted for socio-demographic, clinical predictors and confounding factors, while accounting for competing causes of death. Over a 5-year median follow-up period, 77 deaths occurred among 1,028 patients. Regular/daily cannabis use, elevated coffee intake, and not currently smoking were independently associated with reduced HCV-mortality (adjusted sub-hazard ratio [95%CI]: 0.28[0.10-0.83], 0.38[0.15-0.95], and 0.28[0.10-0.79], respectively). Obesity and severe thinness were associated with increased HCV-mortality (2.44[1.00-5.93] and 7.25[2.22-23.6] *versus* normal weight, respectively). Regular binge drinking was associated with increased non-HCV-mortality (2.19[1.10-4.37]). Further research is needed to understand the causal mechanisms involved. People living with HIV/HCV co-infection should be referred for tobacco, alcohol and weight control interventions and potential benefits of cannabis-based therapies investigated.

Key words

Behavior; substance use; hepatitis C; HIV; mortality

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4 **Introduction**
5

6 Individuals co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV)
7 experience accelerated progression of chronic liver disease[1] and higher mortality[2]. HIV
8 infection has been associated with persistent HCV viremia and reduced response to Peg-interferon-
9 based HCV treatment. Furthermore, it has been hypothesized that HCV infection could interfere
10 with HIV-specific T cells, and thus accelerate HIV progression[3].
11
12

13 Since the introduction of antiretroviral therapy (ART) for HIV, HCV-related complications –
14 mainly end-stage liver disease and hepatocellular carcinoma (HCC) – have become the leading
15 causes of death in HIV/HCV co-infected individuals. Controlling HIV viremia has led to reduced
16 HIV-related mortality, fewer interactions between HCV and HIV, and the emergence of non-HIV-
17 related causes of death[2]. Moreover, the arrival of direct-acting antiviral agents for HCV has
18 resulted in a substantial decrease of many complications associated with liver disease and
19 extrahepatic dysfunction, improving clinical outcomes and patient survival[4]. However, morbidity
20 and mortality remain high due to complications associated with both HCV and HIV, in particular
21 metabolic disorders (e.g., insulin resistance and dyslipidaemia) which are also associated with the
22 occurrence of cardiovascular events[5–7].
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43 In France, the prevalence of HIV/HCV co-infection in people living with HIV was estimated at
44 between 16% and 18% in 2011[8]. Since 2010, the proportion of HCV-related causes of death has
45 increased among co-infected individuals[9–11]. Although HIV/HCV co-infection had been
46 historically linked to intravenous drug use in France[12,13], its prevalence is expected to decrease
47 in this at-risk population[14]. This highlights the importance of investigating other behavioral
48 factors associated with mortality.
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57 Given that almost all co-infected patients can now be cured of HCV infection and that HIV viremia
58 can be controlled, HIV- and HCV-related deaths may compete in different ways in this population.
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4 We hypothesize that specific behaviors can be more predictive of HCV-related mortality today
5
6 than they were before. Accordingly, using data from the French ANRS CO13 HEPAVIH cohort of
7
8 HIV/HCV patients, we made a detailed exploration of the following behaviors, all known to be
9
10 associated with specific comorbidities in HIV/HCV patients: smoking, alcohol consumption,
11
12 coffee consumption and cannabis use.
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16 We investigated smoking for two main reasons. First, it has already been associated with overall
17
18 mortality in the HEPAVIH cohort[15] and accounted for a considerable proportion of the deaths in
19
20 a HIV/HCV cohort study in Canada[16]. Second, the impact of smoking on liver disease
21
22 progression is debatable, as it was not found to be a risk factor for accelerated liver disease in the
23
24 Canadian cohort[17], despite being identified as a risk factor for liver cancer[18]. Alcohol
25
26 consumption is universally recognized as a risk factor for liver disease[19] and its progression[20],
27
28 although it is unknown whether it is a risk factor of HCV-related mortality in HIV/HCV co-infected
29
30 patients[21]. Coffee is widely known to have hepatoprotective properties[22] and, in the HEPAVIH
31
32 population, consumption of three or more cups/day was a major protective factor of overall
33
34 mortality[15]. Cannabis use was previously associated with reduced risk of insulin resistance[23]
35
36 and liver steatosis[24] in HIV/HCV co-infected patients, and also in the general population[25],
37
38 but no significant effect on liver fibrosis has been highlighted[26,27]. We hypothesized that the
39
40 benefits of cannabis can also be observed for HCV-related mortality.
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48 The aim of the present study was to assess the association between the four above-mentioned
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50 behaviors and HCV-related mortality, after adjustment for other behavioral and sociodemographic
51
52 characteristics, while accounting for competing causes of death.
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55 **Methods**

56 **Study design and setting**

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4 ANRS CO13 HEPAVIH is a French hospital-based multicenter prospective cohort, representative
5
6 of the HIV/HCV co-infected population in care nationwide. It included 1,246 patients between
7
8 2005 and 2014. Cohort details were described elsewhere[28]. All patients provided signed
9
10 informed consent at enrolment. The ethics committee of the Cochin University Hospital in Paris
11
12 approved the study protocol[28].
13

14 15 16 **Follow-up and data collection**

17
18 Clinical follow-up visits were scheduled once a year for non-cirrhotic patients, and every six
19
20 months for cirrhotic patients. Physicians filled in a standardized clinical form at each visit, which
21
22 collected data regarding HIV and HCV clinical and biological characteristics and disease
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24 history[28]. Patients' vital status was confirmed by participating centers and, for patients lost to
25
26 follow-up 24 months after enrolment, this information was obtained from the national death
27
28 registry. A medical expert committee validated the classification of causes of death based on
29
30 clinical record review[15]. In addition, patients answered a self-administered questionnaire at
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32 enrolment (M0) and yearly thereafter until 60 months (M60). It collected data on socio-
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34 demographic, psychosocial and behavioral characteristics including the four behaviors under study
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36 here[28].
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43 **Participants and follow-up**

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45 Patients who had at least one completed self-administered questionnaire during follow-up and a
46
47 latest news date (follow-up visit or death) subsequent to their entry date (*i.e.* having at least two
48
49 time points with available information during the cohort follow-up) were eligible for this study.
50
51 The follow-up period for each eligible patient was defined as the period between the first follow-
52
53 up visit with completed self-administered questionnaire (hereafter "baseline visit") and the latest
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55 news date. As self-administered questionnaires were scheduled every 12 months until M60, in
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57 order to study the impact of the covariates measured at each visit on the risk of death during the
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4 subsequent 12 months, the latest news date was censored at 72 months after enrolment. More details
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6 about participant selection are provided elsewhere[15].
7

8 9 **Outcome**

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11 All deaths of eligible patients during the follow-up period were included in this study. We
12
13 performed two separate analyses, the first with the outcome HCV-related deaths, and the second
14
15 with the outcome non-HCV-related deaths (i.e. deaths related to HIV, cancer-related deaths not
16
17 connected to HIV or HCV, and deaths from other causes).
18
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20 21 **Explanatory variables**

22
23 To investigate the association between behaviors and HCV- and non-HCV-related mortality, we
24
25 adjusted for socioeconomic and clinical characteristics known to be associated with the outcome.
26
27 Socioeconomic factors included the following: having a steady partner, being employed, having
28
29 children, and housing comfort and stability. Comfortable housing was defined as reporting “quite
30
31 comfortable” or “very comfortable” *versus* “uncomfortable” or “quite uncomfortable”
32
33 housing[29]. Unstable housing was defined as living in hotels, accommodation centers, on the
34
35 street, or in therapeutic apartments[15]. Clinical variables focused on HCV and HIV and included
36
37 time since HIV and HCV diagnosis, CD4 count, HIV CDC clinical stage, ART, HCV genotype
38
39 and cure. We considered the following HIV transmission categories: injecting drug use (IDU), men
40
41 who have sex with men (MSM), heterosexual/other causes. A history of HCC and/or liver
42
43 transplantation and a history of indirect clinical signs of cirrhosis (ascites, oesophageal varices with
44
45 or without bleeding, or hepatic encephalopathy) were assessed at enrolment. Severe liver fibrosis
46
47 was defined by an FIB-4 index >3.25 (corresponding to an F3-F4 METAVIR score)[30].
48
49 Adherence to ART was assessed using a three-level adherence score (low, moderate, high) based
50
51 on the AIDS Clinical Trial Group methodology[31]. Depressive symptoms were investigated using
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53 the Center for Epidemiological Studies Depression Scale (CES-D), with a score ≥ 17 for men, and
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4 ≥ 23 for women indicating depressive symptoms[32]. Body mass index (BMI) status was defined
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6 by five categories: severely thin (BMI<16), underweight (BMI: 16.0-18.49), normal weight (BMI:
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8 18.49-24.99), overweight (BMI: 25.0-29.9), and obese (BMI ≥ 30).

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11 Drug use was investigated with the question: “During the last four weeks, have you used the
12
13 following drug?” which was followed by a list of drugs. Possible answers to each item were
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15 “never”, “sometimes”, “regularly”, and “daily”. For cannabis/marijuana use we chose a binary
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17 response variable: “regularly/daily” *versus* “never/sometimes”. Patients who answered “never”,
18
19 but who reported to their physician that they smoked at least one joint per day were reclassified as
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21 regular/daily cannabis users. We also tested two variables related to other drug use, namely non-
22
23 prescribed opioid use (heroin, buprenorphine) and stimulant drug use (cocaine, crack, ecstasy,
24
25 amphetamine, LSD and other hallucinogenic drugs).

26
27
28 Smoking status was defined as current smoking *versus* never or past smoking. We used the
29
30 following categories for coffee intake: low (≤ 1 cup/day), moderate (2 cups/day), and elevated (≥ 3
31
32 cups/day)[15]. Alcohol consumption was assessed using the Alcohol Use Disorders Identification
33
34 Test-Consumption questionnaire (AUDIT-C)[33]. One alcohol unit (AU) was defined as a standard
35
36 drink containing 11-14g of alcohol. We used the following categories of alcohol consumption: no
37
38 consumption, low (≤ 1 AU/day), moderate (1–3 AU/day for women; 1–4 AU/day for men), and
39
40 elevated consumption (> 3 AU/day for women; > 4 AU/day for men). Regular binge drinking was
41
42 defined as drinking ≥ 5 AU on one occasion at least once a week.

43
44
45 The time-fixed covariates measured at baseline were: gender, HCV genotype, HIV transmission
46
47 category, history of HCC and/or liver transplantation, history of indirect clinical signs of cirrhosis,
48
49 smoking status, alcohol consumption, regular binge drinking, coffee intake, cannabis use, non-
50
51 prescribed opioid use, and stimulant drug use. We considered baseline measures of behavioral
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53 characteristics in order to avoid the risk of reverse causation. All other explanatory variables were
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4 used as time-varying covariates (measured at each visit). The time-fixed and time-varying
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6 covariates are shown in Tables 3 and 4.
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8 9 **Statistical analyses**

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11 HCV-related and non-HCV-related mortality rates were computed as the number of corresponding
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13 deaths divided by the number of person-years during the study period (computed as the sum, for
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15 all patients, of the number of years between entry date and latest news date, i.e., death, latest follow-
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17 up visit, or censoring). The ‘last observation carried forward’ method was used to impute the
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19 missing values for the time-varying explanatory variables (i.e., at clinical visits without self-
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21 administered questionnaires). We used Fine and Gray’s competing-risk proportional sub-hazards
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23 model[34] with robust standard errors to estimate the effect of behavioral characteristics on HCV-
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25 related and non-HCV-related mortality, adjusting for potential socio-demographic and clinical
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27 predictors and confounding factors.
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33 Explanatory variables with a p-value<0.20 (Wald test) in the univariable analyses were considered
34
35 eligible for inclusion in the multivariable analysis. To account for potential interaction effects
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37 between tobacco and cannabis, and given that both tobacco and HCV cure are major predictors of
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39 overall mortality in this population, we included smoking status and HCV cure in the multivariable
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41 models, irrespective of their p-values in the univariable analyses. We also adjusted the
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43 multivariable models for gender and age, irrespective of p-values.
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48 We used a backward selection procedure based on the Wald test to identify significant variables in
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50 the final multivariable models (p-value≤0.05), separately for HCV-related and non-HCV-related
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52 mortality. The presence of confounding factors was evaluated by testing each non-significant
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54 variable (the tested variable was considered a confounder and included in the final model if at least
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56 one of the coefficients for the other variables changed by more than 25%). Interactions were
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58 assessed by creating interaction terms and adding them to the main effects model, to test for their
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4 significance. The proportional-sub-hazard assumption was tested graphically, using cumulative
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6 incidence functions, and by testing time interactions for each covariate. Stata/SE 14.2 software
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8 (StataCorp LP, College Station, USA) was used for all analyses.

11 **Results**

14 **Study participants**

16 Among the 1,246 patients included in the cohort between 2005 and November 2014, 1,051 had at
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18 least one completed self-administered questionnaire. Of these, 1,028 had a latest news date
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20 subsequent to their entry date, and so were eligible for analyses. With regard to study participants,
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22 722 (70.2%) were men and the principal HIV transmission category was IDU (63.2%). At
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24 enrolment, 31 (3.0%) had a history of HCC and/or liver transplantation, and 30 (2.9%) had a
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26 history of indirect clinical signs of cirrhosis. At the last available visit, median age was 49 years
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28 [interquartile range (IQR) 46-52 years], 972 patients (94.5%) were receiving ART, 566 (55.1%)
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30 had CD4>500 cells/mm³, 162 (15.8%) had severe liver fibrosis (FIB-4>3.25), and 247 (24.0%)
31
32 were cured post-HCV-treatment. With regard to socio-behavioral characteristics measured at
33
34 baseline, 738 patients (71.8%) were current smokers, 274 (26.6%) had elevated coffee intake, 143
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36 (13.9%) were regular binge drinkers, 255 (24.8%) used cannabis regularly or daily, 37 (3.6%) used
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38 non-prescribed opioids, and 87 (8.5%) used stimulant drugs (Table 2).

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45 Among the 1,028 study participants, accounting for 4,700 person-years, 77 deaths occurred over
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47 the median 5-year follow-up period as follows: 33 (42.9%) were HCV-related, 8 (10.4%) were
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49 HIV-related, 9 (11.7%) were cancer-related, and 27 (35.1%) were deaths from other causes. The
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51 distribution of causes of deaths in each category is described in Table 1. Mortality rate per 100
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53 person-years [95% confidence interval (CI)] was 1.64 [1.31-2.05] for all-cause deaths, 0.70 [0.50-
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55 0.99] for HCV-related deaths, and 0.94 [0.70-1.26] for non-HCV-related deaths. Among the 33
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57 HCV-related deaths, 29 (87.9%) occurred in men, 22 (66.7%) in patients with severe fibrosis, and
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4 16 (48·5%) in those with a history of HCC and/or liver transplantation. Patients who died from
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6 HIV-related causes were younger (median age: 45 years) than those who died from other causes
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8 (median age ranged from 48 years in patients who died from HCV-related causes to 50 years in
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10 patients who died from cancer) (Table 2).
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13 **Univariable analyses**

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16 Factors associated with reduced HCV-related mortality were female gender, post-treatment HCV-
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18 cure, HCV genotype 2/3, employment, and elevated coffee intake (Table 3). Factors associated
19
20 with increased HCV-related mortality were a history of HCC and/or liver transplantation, a history
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22 of indirect clinical signs of cirrhosis, severe fibrosis, CD4 count \leq 200 and 200-350, BMI $<$ 16 and
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24 \geq 30, and unstable housing.
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28 With respect to non-HCV-related mortality, post-treatment HCV-cure, having children,
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30 comfortable housing, having a steady partner, and being employed were all associated with reduced
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32 non-HCV-related mortality. By contrast, HIV CDC clinical stage C, regular binge drinking and
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34 unstable housing were all associated with increased non-HCV-related mortality.
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38 No association was found for either non-prescribed opioid use or stimulant drug use at baseline
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40 and both HCV-related and non-HCV-related mortality (Table 3).
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43 **Multivariable analysis**

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45 In the multivariable analysis (Table 4), regular or daily cannabis use was associated with decreased
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47 HCV-related mortality (adjusted sub-hazard ratio (aSHR) [95% CI]: 0·28[0·10-0·83]), as well as
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49 never or past smoking and elevated coffee intake (0·28[0·10-0·79] and 0·38[0·15-0·95],
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51 respectively).
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55 In contrast, a history of HCC and/or liver transplantation was associated with increased HCV-
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57 related mortality (15·1[4·68-49·0]). This was also true for severe thinness and obesity (7·25[2·22-
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59 23·6] and 2·44[1·00-5·93], respectively, *versus* normal weight), CD4 count \leq 200 and 200-350
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4 (5.24[1.99-13.8] and 3.30[1.23-8.84], respectively, *versus* CD4>500), and a history of indirect
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6 clinical signs of cirrhosis (4.46[1.55-12.8]).
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9 With regard to non-HCV-related deaths, having a steady partner and comfortable housing were
10
11 independently associated with reduced non-HCV-related mortality (0.48[0.26-0.90] and
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13 0.51[0.26-0.99], respectively). Furthermore, HIV CDC clinical stage C and regular binge drinking
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15 were associated with increased non-HCV-related mortality (2.87[1.53-5.37] and 2.19[1.10-4.37],
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17 respectively).
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21 Interestingly, being cured after HCV treatment was not associated with either HCV-related or non-
22
23 HCV-related mortality. We found no indication that the proportionality assumption was violated
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25 (Figure 1), and no significant interaction in the multivariable models.
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28 **Discussion**

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30 This study is the first to explore the role of cannabis use on HCV-related mortality using a
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32 competing-risk approach in HIV/HCV co-infected patients while adjusting for other behavioral
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34 and clinical factors. In a previous investigation on the same cohort, elevated coffee consumption
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36 (≥ 3 cups/day) was associated with a 50% reduced all-cause mortality risk[15]. The present study
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38 showed – after adjustment for HCV cure and immune restoration (measured by CD4 count) – an
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40 independent association between coffee intake and decreased HCV-related mortality in co-infected
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42 patients, and revealed two other behavioral factors associated with reduced HCV-related mortality:
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44 regular/daily cannabis use and never/past tobacco smoking. These results are important as they
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46 suggest that social interventions and behavioral changes can further decrease HCV-related
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48 mortality in this population.
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55 The main innovation of this study is the competing-risk approach used to analyze deaths related to
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57 HCV in the presence of competing deaths related to HIV, cancer and other causes. This is
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4 particularly pertinent today given that a HCV cure exists and that greater knowledge is needed
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6 about risk factor patterns of competing causes of death in HIV/HCV co-infected individuals.
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9 Our results concerning cannabis use are consistent with previous investigations. Cannabidiol – a
10 non-psychoactive component of cannabis – has demonstrated antioxidant and anti-inflammatory
11 effects which reduce liver damage by attenuating hepatic ischemia-reperfusion[35]. Furthermore,
12 two different studies highlighted that daily cannabis use was associated with lower prevalence of
13 steatosis[24] and was not associated with fibrosis or cirrhosis progression[36,37]. Considering that
14 insulin resistance (IR) has been associated with a higher risk of HCC in chronic HCV infection[38],
15 we hypothesize that the inverse association between cannabis use and HCV-related mortality is the
16 result of the lower risk of developing IR[23], and the possible association between cannabinoids
17 (contained in cannabis) and anti-proliferative stimulation in HCC[39].
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31 The independent association we found between elevated coffee intake and decreased HCV-related
32 mortality is also consistent with previous findings, which correlated coffee consumption with a
33 lower risk of death from all causes in people with HIV/HCV co-infection[15]. This
34 hepatoprotective effect of elevated coffee intake is probably due to anti-inflammatory properties
35 of certain coffee compounds, such as polyphenols[40,41]. It is also possible that coffee intake is a
36 confounder of other clinical conditions given that elevated coffee consumption has been directly
37 associated with reduced IR and lower levels of liver fibrosis[41], and inversely associated with
38 abnormal liver enzymes[40].
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50 Furthermore, the association we found between never or past smoking and reduced HCV-related
51 mortality is in line with previous evidence that smoking is associated with excess all-cause
52 mortality in HIV/HCV co-infected individuals[42]. The reduced risk of HCV-related deaths for
53 non-current smokers underlines the importance of tobacco cessation in this population for
54 improved survival.
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4 Previous studies already highlighted an inverse association between CD4 count and progression to
5 advanced liver fibrosis in HIV/HCV co-infected patients[1]. In the present study, we demonstrated
6 that lower CD4 levels were associated with increased HCV-related mortality, even after controlling
7 for clinical signs of cirrhosis and history of HCC. HIV CDC clinical stage C was associated with
8 increased non-HCV-related mortality. This finding is most likely due to HIV disease progression,
9 and confirms previous findings that higher CD4 counts are associated with lower risk of clinical
10 events and deaths[1].
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21 Other studies have identified advanced liver fibrosis and HCC as predictors of liver-related deaths
22 in HIV/HCV co-infected patients[2]. Likewise, our study found an independent association
23 between HCV-related mortality and a history of clinical signs of cirrhosis and HCC/liver
24 transplantation, after accounting for competing causes of death. Moreover, achieving sustained
25 virological response after HCV treatment has been associated with extended survival in patients
26 with compensated cirrhosis[4]. However, in our study we did not find a significant association
27 between HCV cure and either HCV-related or non-HCV-related mortality in multivariable analysis.
28 The lack of long-term data after HCV treatment may explain this result. However, even though
29 HCV cure has been associated with reduced HCC incidence after HCV-treatment, and with a lower
30 relative reduction of HCC risk in patients with cirrhosis[43], the results in our population suggest
31 that severe complications of liver disease are more predictive of death, and underline the
32 importance of early HCV treatment in HIV/HCV co-infection.
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50 Our findings regarding BMI are consistent with previous results highlighting the association
51 between both overweightness and obesity and all-cause mortality[44]. Additionally, we found that
52 severe thinness is associated with HCV-related mortality. We hypothesize that this can be
53 explained by the increased risk of cardiovascular events associated with severe thinness in our
54 population. Another study found that a BMI below 18.5 was associated with increased all-cause
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4 mortality in the general population[45] and may be a potential independent risk factor for
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6 cardiovascular disease[46].
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9 Having a steady partner was associated with lower non-HCV-related mortality. This result is
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11 consistent with previous investigations showing that having no partner was associated with an
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13 increased mortality rate when compared with having a steady partner, after accounting for various
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15 aspects of social network and for socioeconomic status[47]. The association between comfortable
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17 housing and reduced non-HCV-related mortality may be explained by considering housing
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19 conditions as a determinant of health. One systematic review concluded that improving housing
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21 conditions not only promotes better health outcomes, but also enhances determinants of health,
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23 such as diet and social relationships[48].
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28 At last, we found an association between regular binge drinking and non-HCV-related mortality.
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30 This is consistent with studies showing that binge drinking is independently associated with
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32 increased all-cause mortality[49]. Given that alcohol misuse is often under-reported among
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34 HIV/HCV co-infected individuals[21], individuals at higher risk were probably not identified in
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36 our population, and so no association was found between elevated alcohol consumption and the
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38 outcome. Elsewhere, excessive alcohol consumption was associated with younger age at death in
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40 HCV/HIV co-infected individuals, which would suggest that this population is at greater risk of
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42 premature death[50].
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47 This study has strengths and limitations. The major strength is that it is based on one of the rare
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49 cohorts of HIV/HCV co-infected individuals combining detailed clinical follow-up data with socio-
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51 behavioral data based on yearly self-administered questionnaires. Moreover, it is one of the few
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53 studies to use a competing-risk model to investigate cause-specific mortality in the presence of
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55 competing events. The study's limitations are attributable to self-reported data, which may be a
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57 source of underreporting of some behaviors due to social desirability bias. However, previous
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4 studies have already shown that self-administered questionnaires capture behavioral data better
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6 than face-to-face interviews[51]. We recognize that there is no standard scale to measure cannabis
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8 use and that the available instruments focus on the assessment of cannabis misuse and
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10 disorders[52]. Accordingly, we may have underestimated cannabis consumption. Nevertheless, to
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12 minimize potential biases, we also considered the information provided in medical interviews.
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14 Although we cannot generalize our findings to all the HIV/HCV co-infected population, the
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16 HEPAVIH cohort is likely to be highly representative of co-infected individuals in France, given
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18 that the French healthcare system guarantees free access to HIV and HCV care.
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22 Our findings bring new knowledge to clinical practice and public health promotion for HIV/HCV
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24 co-infected individuals. Elevated coffee consumption, regular/daily cannabis use and never/past
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26 smoking were all independently associated with reduced HCV-related mortality. In contrast, severe
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28 thinness and obesity were associated with increased HCV-related, and binge drinking with
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30 increased non-HCV-related mortality. Addressing these factors may improve survival in HIV/HCV
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32 co-infected individuals, irrespective of HCV cure.
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36 37 38 **Conclusions**

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40 HIV/HCV co-infected individuals should be advised about the benefits of coffee consumption.
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42 Tobacco cessation, as well as alcohol and weight control interventions should be routinely
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44 integrated into clinical practice and public health programs, by motivating patients to reduce risks
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46 associated with these behaviors and referring them to other specialists in the healthcare network.
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50 We recommend that further research be developed to elucidate the causal mechanisms of the factors
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52 identified in this study as being significantly associated with HCV-related and non-HCV-related
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54 mortality. Finally, considering the association between cannabis use and reduced HCV-related
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56 mortality, we believe that a more in-depth assessment of the benefits of cannabis-based therapies
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58 be carried out for the HIV/HCV co-infected population.
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Figures

Figure 1. Covariate-adjusted cumulative incidence function of HCV-related deaths according to coffee intake at baseline (competing-risk regression, multivariable analysis, the ANRS CO13 HEPAVIH cohort)

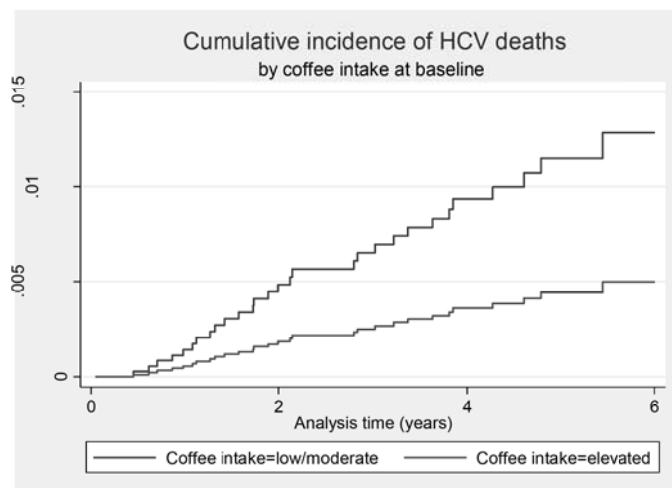


Figure 2. Covariate-adjusted cumulative incidence function of HCV-related deaths according to cannabis use at baseline (competing-risk regression, multivariable analysis, the ANRS CO13 HEPAVIH cohort)

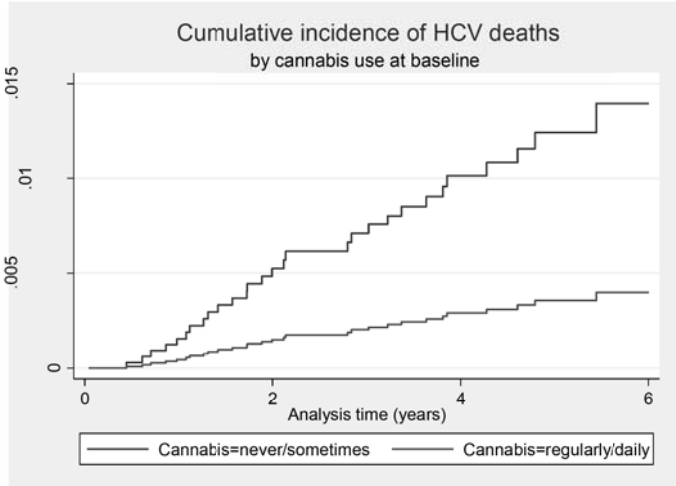
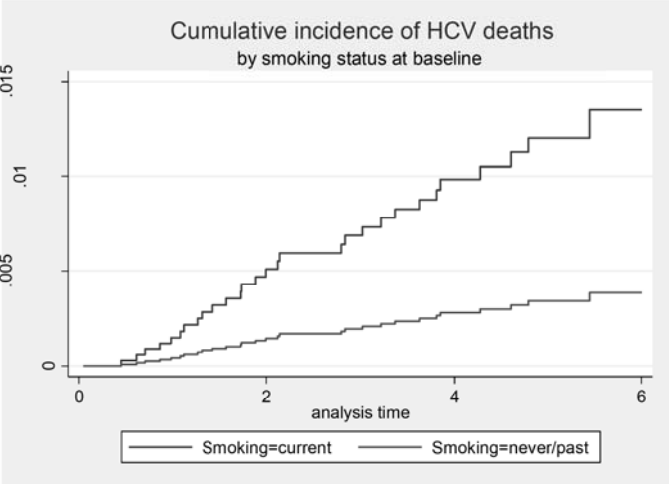


Figure 3. Covariate-adjusted cumulative incidence function of HCV-related deaths according to smoking status at baseline (competing-risk regression, multivariable analysis, the ANRS CO13 HEPAVIH cohort)



Tables**Table I. Total number of deaths by cause (the ANRS CO13 HEPAVIH cohort, n=1,028)**

Total number of deaths by cause	n (%)
HCV-related deaths (including liver cancer)	33 (42·8)
Decompensated cirrhosis	19 (24·7)
Liver cancer	7 (9·1)
Liver cancer & decompensated cirrhosis	4 (5·2)
Complication of liver transplantation	3 (3·9)
Cancer-related deaths (excluding HIV- and HCV-related)	9 (11·7)
Lung and bronchial cancer	5 (6·5)
Pancreatic cancer	1 (1·3)
Colon cancer	1 (1·3)
Cancer of the esophagus	1 (1·3)
Polymetastatic Merkel carcinoma	1 (1·3)
HIV-related deaths	8 (10·4)
Progressive multifocal leukoencephalopathy	4 (5·2)
Hodgkin's lymphoma	1 (1·3)
HIV encephalitis	1 (1·3)
HIV-associated pulmonary arterial hypertension	1 (1·3)
HIV-associated opportunistic pneumonias	1 (1·3)
Deaths from other causes	27 (35·1)
Unknown	11 (14·3)
Cardiovascular disease	3 (3·9)

Overdose	3 (3·9)
Suicide	3 (3·9)
Respiratory diseases	2 (2·6)
Unexplained sudden death	2 (2·6)
Infectious and parasitic diseases	1 (1·3)
Digestive diseases	1 (1·3)
Endocrine, nutritional and metabolic diseases	1 (1·3)
Total	77 (100)

Table II. Characteristics of the study population measured at last available follow-up visit according to specific causes of death (the ANRS CO13 HEPAVIH cohort, n=1,028)

		n (%) of patients	HCV-related deaths (n=33)	HIV-related deaths (n=8)	Cancer - related deaths (n=9)	Deaths from other causes (n=27)	Total deaths (n=77)
Gender	Male	722 (70.2)	29	5	5	22	61
	Female	306 (29.8)	4	3	4	5	16
Age (years)[§]	18-39	50 (4.9)	1	0	0	1	2
	40-49	531 (51.6)	18	7	4	19	48
	50+	447 (43.5)	14	1	5	7	27
Age (years)[§]	<i>Median [IQR]</i>	<i>49 [46-52]</i>	<i>48 [45-52]</i>	<i>45 [44-47]</i>	<i>50 [46-53]</i>	<i>48 [43-50]</i>	<i>48 [44-51]</i>
Having a steady partner[§]	No	395 (38.4)	16	6	5	13	40
	Yes	628 (61.1)	17	2	4	14	37
	Missing	5 (0.5)	0	0	0	0	0
Being employed[§]	No	536 (52.1)	25	4	5	20	54
	Yes	487 (47.4)	8	4	4	7	23
	Missing	5 (0.5)	0	0	0	0	0
Having children[§]	No	715 (69.5)	24	8	6	22	60
	Yes	310 (30.2)	9	0	3	4	16
	Missing	3 (0.3)	0	0	0	1	1

Comfortable housing[§]	No	166 (16·1)	8	1	1	12	22
	Yes	860 (83·7)	25	7	8	15	55
	Missing	2 (0·2)	0	0	0	0	0
Unstable housing^{§a}	No	1006 (97·9)	30	8	8	25	71
	Yes	18 (1·7)	3	0	1	2	6
	Missing	4 (0·4)	0	0	0	0	0
HCV genotype	1/4	755 (73·4)	30	5	7	19	61
	2/3	260 (25·3)	3	3	2	8	16
	Missing	13 (1·3)	0	0	0	0	0
Post-treatment HCV cure[§]	No	781 (76·0)	32	8	9	24	73
	Yes	247 (24·0)	1	0	0	3	4
Severe fibrosis (FIB-4>3·25)[§]	No	844 (82·1)	9	7	8	21	40
	Yes	162 (15·8)	22	1	0	4	27
	Missing	22 (2·1)	2	0	1	2	2
History of HCC and/or liver transplantation at enrollment^{§§}	No	997 (97·0)	17	7	9	25	58
	Yes	31 (3·0)	16	1	0	2	19
History of indirect clinical signs of cirrhosis at enrollment^{§§b}	No	998 (97·1)	22	7	9	26	64
	Yes	30 (2·9)	11	1	0	1	13

HIV transmission category	IDU	650 (63·2)	27	6	6	16	55
	MSM/bisexual	117 (11·4)	1	1	0	3	5
	Heterosexual	144 (14·0)	3	0	3	4	10
	Other	114 (11·1)	2	1	0	4	7
	Missing	3 (0·3)	0	0	0	0	0
Time since HCV diagnosis (years)[§]	<i>Median [IQR]</i>	<i>14 [10-18]</i>					
Time since HIV diagnosis (years)[§]	<i>Median [IQR]</i>	<i>22 [17-25]</i>					
HIV CDC clinical stage[§]	A	460 (44·7)	9	1	1	7	18
	B	268 (26·1)	10	2	3	6	21
	C	297 (28·9)	14	5	4	14	37
	Missing	3 (0·3)	0	0	1	0	1
ART-treated[§]	No	52 (5·1)	4	0	1	1	6
	Yes	972 (94·5)	29	8	8	26	71
	Missing	4 (0·4)	0	0	0	0	0
Adherence to ART[§]	Low	140 (13·6)	2	2	2	3	9
	Moderate	175 (17·0)	6	0	1	5	12
	High	652 (63·4)	21	6	5	18	50
	Not treated	52 (5·1)	4	0	1	1	6
	Missing	9 (0·9)	0	0	0	0	0
CD4 count (cells/mm³)[§]	≤200	84 (8·2)	12	2	0	5	19
	200-350	159 (15·5)	8	2	2	6	18

	350-500	219 (21·3)	6	2	1	5	14
	>500	566 (55·1)	7	2	6	11	26
Depressive symptoms^{§c}	No	612 (59·5)	15	4	6	13	38
	Yes	375 (36·5)	14	4	3	12	33
	Missing	41 (4·0)	4	0	0	2	6
Smoking status at baseline^{§§}	Never/past	272 (26·5)	8	2	1	4	15
	Current	738 (71·8)	24	6	7	22	59
	Missing	18 (1·7)	1	0	1	1	3
Alcohol consumption at baseline^{§§d}	No consumption	256 (24·9)	11	2	3	8	24
	Low	502 (48·8)	9	4	3	12	28
	Moderate	183 (17·8)	8	1	1	3	13
	Elevated	61 (5·9)	4	1	2	3	10
	Missing	26 (2·5)	1	0	0	1	2
Regular binge drinking at baseline^{§§e}	No	842 (81·9)	26	6	7	16	55
	Yes	143 (13·9)	5	2	2	9	18
	Missing	43 (4·2)	2	0	0	2	4
Coffee intake at baseline^{§§f}	Low	527 (51·3)	24	5	5	11	45
	Moderate	227 (22·1)	6	1	3	11	21
	Elevated	274 (26·6)	3	2	1	5	11
Cannabis use at baseline^{§§}	Never	471 (45·8)	17	2	3	10	32
	Sometimes	203 (19·7)	9	1	1	7	18
	Regularly/daily	255 (24·8)	4	4	4	6	18
	Missing	99 (9·6)	3	1	1	4	9

Non-prescribed opioid use at baseline^{§§}	No	907 (88·2)	28	7	9	21	65
	Yes	37 (3·6)	2	0	0	2	4
	Missing	84 (8·2)	3	1	0	4	8
Stimulant drug use at baseline^{§§}	No	857 (83·4)	29	7	9	20	65
	Yes	87 (8·5)	1	0	0	3	4
	Missing	84 (8·2)	3	1	0	4	8
Body mass index status[§]	Severely thin (BMI<16)	19 (1·8)	2	0	1	0	3
	Underweight (BMI: 16-18·49)	110 (10·7)	2	2	2	1	7
	Normal weight (BMI: 18·5-24·99)	658 (64·0)	21	3	6	18	48
	Overweight (BMI: 25-29·99)	192 (18·7)	4	3	0	6	13
	Obese (BMI≥30)	48 (4·7)	4	0	0	2	6
	Missing	1 (0·1)	0	0	0	0	0

CI=confidence interval; IQR=interquartile range.

[§] Time-varying variable, descriptive statistics are given for the last available visit of each patient.

^{§§} Fixed variable, measured at baseline (i.e. at the first available visit of each patient).

^a Patients who reported living in hotels, accommodation centers, on the street or in therapeutic apartments were considered to have unstable housing.

^b The presence of indirect clinical signs of cirrhosis was defined by one of the following: ascites, esophageal varices with or without bleeding, hepatic encephalopathy.

^c Patients with a CES-D score $\geq 17(23)$ for men(women) were considered to have depressive symptoms.

^d The following categories were used for average daily alcohol consumption: no consumption, low (≤ 1 alcohol unit (AU)/day), moderate (1–3 AU/day for women, and 1–4 AU/day for men), and elevated (> 3 AU/day for women, and > 4 AU/day for men).

^e Regular binge drinking was defined as drinking at least 5 AU on one occasion at least once a week.

^f We used the following categories for average daily coffee intake: low (≤ 1 cups/day), moderate (2 cups/day), and elevated (≥ 3 cups/day).

Table III. Factors associated with HCV-related and non-HCV-related mortality
(competing-risk regression models, univariable analyses, the ANRS CO13 HEPAVIH
cohort, n=1,028 patients, N=4,579 visits)

		HCV-related mortality		Non-HCV-related mortality	
		SHR [95% CI]	p-value	SHR [95% CI]	p-value
Gender	Male (ref)	1		1	
	Female	0.32 [0.11-0.92]	0.034	0.88 [0.45-1.71]	0.710
Age (years)[§]	18-39	0.44 [0.06-3.33]	0.431	0.27 [0.04-2.01]	0.202
	40-49 (ref)	1		1	
	50+	1.48 [0.73-3.02]	0.274	0.74 [0.38-1.42]	0.365
Age (years)[§]		1.03 [0.99-1.08]	0.142	1.02 [0.97-1.07]	0.455
Having a steady partner[§]	No (ref)	1		1	
	Yes	0.63 [0.32-1.25]	0.185	0.49 [0.27-0.89]	0.020
Being employed[§]	No (ref)	1		1	
	Yes	0.33 [0.15-0.73]	0.006	0.54 [0.29-1.02]	0.057
Having children[§]	No (ref)	1		1	
	Yes	0.79 [0.37-1.70]	0.546	0.40 [0.18-0.91]	0.028
Comfortable housing[§]	No (ref)	1		1	
	Yes	0.62 [0.28-1.37]	0.242	0.42 [0.22-0.78]	0.007
Unstable housing^{§a}	No (ref)	1		1	
	Yes	5.22 [1.67-16.3]	0.004	4.09 [1.27-13.2]	0.018
HCV genotype	1/4 (ref)	1		1	
	2/3	0.29 [0.09-0.95]	0.040	1.24 [0.65-2.37]	0.516

Post-treatment HCV cure[§]	No (ref)	1		1	
	Yes	0.12 [0.02-0.88]	0.037	0.27 [0.08-0.85]	0.025
Severe fibrosis (FIB-4>3.25)[§]	No (ref)	1		1	
	Yes	13.33 [6.13-29.0]	<10 ⁻³	0.60 [0.24-1.51]	0.280
History of HCC and/or liver transplantation at enrollment^{§§}	No (ref)	1		1	
	Yes	38.9 [19.6-76.9]	<10 ⁻³	2.21 [0.70-6.94]	0.173
History of indirect clinical signs of cirrhosis at enrollment^{§§b}	No (ref)	1		1	
	Yes	20.4 [9.97-41.7]	<10 ⁻³	1.57 [0.39-6.29]	0.521
HIV transmission category	IDU (ref)	1		1	
	MSM/bisexual	0.21 [0.03-1.52]	0.121	0.81 [0.29-2.32]	0.700
	Heterosexual	0.49 [0.15-1.61]	0.239	1.10 [0.48-2.53]	0.816
	Other	0.40 [0.09-1.70]	0.216	0.96 [0.37-2.49]	0.940
Time since HCV diagnosis (years)[§]		0.96 [0.90-1.02]	0.221	1.00 [0.95-1.05]	0.922
Time since HIV diagnosis (years)[§]		1.00 [0.96-1.04]	0.946	0.98 [0.94-1.03]	0.433

HIV CDC clinical stage [§]	A/B (ref)	1		1	
	C	1·87 [0·94-3·73]	0·073	2·95 [1·62-5·36]	<10 ⁻³
ART-treated [§]	No (ref)	1		1	
	Yes	0·46 [0·16-1·32]	0·150	1·32 [0·32-5·47]	0·698
Adherence to ART [§]	Low (ref)	1		1	
	Moderate	1·66 [0·35-7·89]	0·526	0·49 [0·16-1·45]	0·199
	High	1·65 [0·40-6·84]	0·486	0·67 [0·30-1·52]	0·342
	Not treated	3·42 [0·64-18·3]	0·151	0·51 [0·11-2·41]	0·393
CD4 count (cells/mm³) [§]	>500 (ref)	1		1	
	350-500	2·01 [0·68-5·95]	0·204	1·01 [0·44-2·29]	0·983
	200-350	3·23 [1·17-8·89]	0·023	1·52 [0·71-3·28]	0·281
	≤200	11·2 [4·47-28·3]	<10 ⁻³	2·29 [0·96-5·45]	0·060
Depressive symptoms ^{§c}	No (ref)	1		1	
	Yes	1·48 [0·71-3·06]	0·290	1·30 [0·71-2·38]	0·401
Smoking status at baseline ^{§§}	Current (ref)	1		1	
	Never/past	0·87 [0·39-1·94]	0·733	0·51 [0·23-1·15]	0·107
Alcohol consumption at baseline ^{§§d}	No consumption (ref)	1		1	
	Low	0·42 [0·17-1·01]	0·052	0·75 [0·37-1·51]	0·419
	Moderate	1·02 [0·41-2·52]	0·971	0·54 [0·19-1·50]	0·238
	Elevated	1·55 [0·49-4·87]	0·452	2·00 [0·76-5·26]	0·159
Regular binge drinking at baseline ^{§§e}	No (ref)	1		1	
	Yes	1·11 [0·42-2·88]	0·834	2·66 [1·38-5·11]	0·003
Coffee intake at baseline ^{§§f}	Low/moderate (ref)	1		1	
	Elevated	0·27 [0·08-0·88]	0·030	0·60 [0·28-1·30]	0·199

Cannabis use at baseline^{§§}	Never/sometimes (ref)	1		1	
	Regularly/daily	0.39 [0.13-1.11]	0.077	1.50 [0.77-2.92]	0.228
Non-prescribed opioid use at baseline^{§§}	No (ref)	1		1	
	Yes	1.76 [0.41-7.61]	0.449	1.30 [0.31-5.40]	0.717
Stimulant drug use at baseline^{§§}	No (ref)	1		1	
	Yes	0.36 [0.05-2.64]	0.315	0.90 [0.27-2.93]	0.856
Body mass index status[§]	Severely thin (BMI<16)	5.10 [1.25-20.8]	0.023	1.76 [0.23-13.4]	0.587
	Underweight (BMI: 16-18.49)	0.54 [0.13-2.33]	0.411	1.08 [0.42-2.78]	0.878
	Normal weight (BMI: 18.5-24.99) (ref)	1		1	
	Overweight (BMI: 25-29.99)	0.70 [0.24-2.04]	0.520	1.23 [0.58-2.61]	0.582
	Obese (BMI≥30)	3.50 [1.20-10.2]	0.021	1.20 [0.29-4.92]	0.801

CI=confidence interval; SHR=sub-hazard ratio.

§ Time-varying variable, descriptive statistics are given for the last available visit of each patient.

§§ Fixed variable, measured at baseline (i.e. at the first available visit of each patient).

* With robust standard errors

^a Patients who reported living in hotels, accommodation centers, on the street or in therapeutic apartments were considered to have unstable housing.

^b The presence of indirect clinical signs of cirrhosis was defined by one of the following: ascites, esophageal varices with or without bleeding, hepatic encephalopathy.

^c Patients with a CES-D score $\geq 17(23)$ for men(women) were considered to have depressive symptoms.

^d The following categories were used for average daily alcohol consumption: no consumption, low (≤ 1 alcohol unit (AU)/day), moderate (1–3 AU/day for women and 1–4 AU/day for men), and elevated (>3 AU/day for women and >4 AU/day for men).

^e Regular binge drinking was defined as drinking at least 5 AU on one occasion at least once a week.

^f We used the following categories for average daily coffee intake: low (≤ 1 cups/day), moderate (2 cups/day), and elevated (≥ 3 cups/day).

Table IV. Factors associated with HCV-related and non-HCV-related mortality (competing-risk regression models, multivariable analysis, the ANRS CO13 HEPAVIH cohort)

		HCV-related mortality (n=910 patients, N=4,036 visits)		Non-HCV-related mortality (n=974 patients, N=4,341 visits)	
		aSHR [95% CI]	p-value	aSHR [95% CI]	p-value
Gender	Male (ref)	1		1	
	Female	0.31 [0.06-1.45]	0.136	0.99 [0.49-1.98]	0.979
Age (years)[§]		0.98 [0.92-1.05]	0.619	1.01 [0.96-1.06]	0.782
Having a steady partner[§]	No (ref)			1	
	Yes			0.48 [0.26-0.90]	0.022
Comfortable housing[§]	No (ref)			1	
	Yes			0.51 [0.26-0.99]	0.047
Post-treatment HCV cure[§]	No (ref)	1		1	
	Yes	0.26 [0.03-1.84]	0.176	0.32 [0.10-1.01]	0.052
History of HCC and/or liver transplantation at enrollment^{§§}	No (ref)	1			
	Yes	15.1 [4.68-49.0]	<10 ⁻³		
History of indirect clinical signs of	No (ref)	1			
	Yes	3.96 [1.28-12.3]	0.017		

cirrhosis at enrollment ^{§§a}					
HIV CDC clinical stage [§]	A/B (ref) C			1 2·87 [1·53-5·37]	0·001
CD4 count (cells/mm³) [§]	>500 (ref) 350-500 200-350 ≤200	1 2·21 [0·73-6·70] 3·30 [1·23-8·84] 5·24 [1·99-13·8]	0·162 0·017 0·001		
Smoking status at baseline ^{§§}	Current (ref) Never/past	1 0·28 [0·10-0·79]	0·016		
Regular binge drinking at baseline ^{§§b}	No (ref) Yes			1 2·19 [1·10-4·37]	0·026
Coffee intake at baseline ^{§§c}	Low/moderate (ref) Elevated	1 0·38 [0·15-0·95]	0·040		
Cannabis use at baseline ^{§§}	Never/sometimes (ref) Regularly/daily	1 0·28 [0·10-0·83]	0·021		
Body mass index [§]	Severely thin (BMI<16) Underweight (BMI: 16-18·49) Normal weight (BMI: 18·5-24·99) (ref) Overweight (BMI: 25-29·99) Obese (BMI≥30)	7·25 [2·22-23·6] 0·49 [0·06-3·86] 1 0·67 [0·23-1·96] 2·44 [1·00-5·93]	0·001 0·497 0·464 0·049		

aSHR=adjusted sub-hazard ratio; CI=confidence interval; SHR=sub-hazard ratio.

§ Time-varying variable.

§§ Fixed variable, measured at baseline (i.e. at the first available visit of each patient).

* With robust standard errors

^a The presence of indirect clinical signs of cirrhosis was defined by one of the following: ascites, esophageal varices with or without bleeding, hepatic encephalopathy.

^b Regular binge drinking was defined as drinking at least 5 AU on one occasion at least once a week.

^c We used the following categories for average daily coffee intake: low (≤ 1 cups/day), moderate (2 cups/day), and elevated (≥ 3 cups/day).