



HAL
open science

Direct, indirect and total effect of HIV coinfection on the risk of non-liver-related cancer in hepatitis C virus-infected patients treated by direct-acting antivirals: a mediation analysis

Mathieu Chalouni, Stanislas Pol, Philippe Sogni, Helene Fontaine, Karine Lacombe, Jean-Marc Lacombe, Laure Esterle, Celine Dorival, Marc Bourliere, Firouze Bani-Sadr, et al.

► To cite this version:

Mathieu Chalouni, Stanislas Pol, Philippe Sogni, Helene Fontaine, Karine Lacombe, et al.. Direct, indirect and total effect of HIV coinfection on the risk of non-liver-related cancer in hepatitis C virus-infected patients treated by direct-acting antivirals: a mediation analysis. *HIV Medicine*, 2021, 22 (10), pp.924-935. 10.1111/hiv.13153 . hal-03361010

HAL Id: hal-03361010

<https://hal.science/hal-03361010v1>

Submitted on 1 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1
2
3 **Direct, indirect and total effect of HIV co-infection on the risk of non-**
4 **liver-related cancer in hepatitis C virus infected patients treated by**
5 **direct-acting antivirals: a mediation analysis**
6
7
8
9

10
11 **Running head:** HIV co-infection effects on cancers risk
12

13 M. Chalouni ¹, S. Pol ²⁻³, P. Sogni ²⁻³, H. Fontaine ², K. Lacombe ⁴⁻⁵, JM. Lacombe ⁶, L.
14 Esterle ¹, C. Dorival ⁴, M. Bourlière ⁷, F. Bani-Sadr ⁸, V. de Ledinghen ⁹⁻¹⁰, D. Zucman
15 ¹¹, D. Larrey ¹², D. Salmon ³⁻¹³, F. Carrat ⁴⁻¹⁴, L. Wittkop ¹⁻¹⁵ for the ANRS CO13
16 HEPAVIH and ANRS CO22 HEPATHER cohorts study groups \$
17
18
19
20
21

22 **Affiliations**
23

24
25 ¹ Univ. Bordeaux, ISPED, Inserm, Bordeaux Population Health Research Center, team
26 MORPH3EUS, UMR 1219, CIC-EC 1401, F-3300 Bordeaux, France
27

28
29 ² Université de Paris ; Assistance Publique - Hôpitaux de Paris Centre, Hôpital Cochin,
30 Département d'Hépatologie ; INSERM U-1223, Institut Pasteur, Paris, France
31

32
33 ³ Université de Paris, Paris, France
34

35
36 ⁴ Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé
37 Publique, IPLESP, F75012, Paris, France
38

39
40 ⁵ APHP. Est, Hôpital Saint-Antoine, Service de Maladies Infectieuses et Tropicales,
41 Paris, F75012, France
42
43

44
45 ⁶ INSERM Transfert, Paris, France
46

47
48 ⁷ Department of Hepatology and Gastroenterology, Hôpital Saint Joseph, Marseille,
49 France
50

51
52 ⁸ Department of Internal Medicine, Clinical Immunology and Infectious Diseases,
53 Robert Debré Hospital, University Hospital, Reims, France
54

55
56 ⁹ Centre Hospitalier Universitaire de Bordeaux, Hôpital Haut-Lévêque, Service
57 d'Hépatologie, Bordeaux, France
58
59
60

1
2
3 ¹⁰ INSERM U1053, Université de Bordeaux, Bordeaux, France
4

5 ¹¹ Hôpital Foch, service de médecine interne, Suresnes, France
6

7 ¹² Service des maladies de l'appareil digestif, Hôpital Saint Eloi, IBR- Inserm
8

9 Montpellier, France
10

11 ¹³ Service Maladies infectieuses et tropicales, AP-HP. Centre, Hôpital Cochin Hôtel
12

13 Dieu, Paris, France
14

15 ¹⁴ AP-HP. Est, Hôpital Saint-Antoine, Unité de Santé Publique, Paris, France
16

17 ¹⁵ CHU de Bordeaux, Pôle de santé publique, F-33000 Bordeaux, France
18

19 \$ listed in the Acknowledgements
20
21

22
23
24 **Corresponding author:**
25

26 Mathieu Chalouni
27

28 Address: 146 rue Léo Saignat, CS61292, 33076 Bordeaux cedex, France
29

30 Telephone number: +33 (0)5 57 57 45 26
31

32 Fax number: 33 (0)5 56 24 00 81
33

34 **Word count:** 3499
35

36 **Number of figures and tables:** 5
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Objectives: HIV co-infected patients experience higher incidences of non-liver-related cancers than HCV mono-infected patients. Chronic inflammation, immunosuppression, but also higher tobacco or alcohol consumption and metabolic dysregulation could explain this higher risk. We aimed to estimate the direct, indirect and total effects of HIV co-infection on the risk of non-liver-related cancers in HCV participants treated by DAA.

Methods: Up to 4 HCV mono-infected participants from the ANRS CO22 HEPATHER cohort were matched by age and sex to HIV/HCV co-infected participants from the ANRS CO13 HEPAVIH cohort. Participants were followed from DAA initiation until the occurrence of a non-liver-related cancer. Counterfactual mediation analysis was carried out to estimate the direct (chronic inflammation and immunosuppression), indirect (tobacco and alcohol consumption and metabolic syndrome) and total effect of HIV co-infection on the risk of non-liver-related cancers.

Results: 548 HIV/HCV co-infected and 2016 mono-infected participants were included. Overall, HIV co-infection was associated with a 3.7 times 95% CI [1.7; 7.0] higher risk of non-liver-related cancers in HCV participants. This increased risk was explained by significant direct effect (HR: 3.4 95% CI: [1.7; 6.6]) but not indirect effect (HR: 1.1 95% CI: [0.8; 1.5]) of HIV co-infection.

Conclusions: In HCV participants treated by DAA, the direct effect of HIV co-infection, reflecting chronic inflammation and immunosuppression, was associated with a 3.7 times higher risk of non-liver-related. In contrast, the indirect effect of HIV co-infection, reflecting higher tobacco and alcohol consumption and metabolic dysregulation, was not significantly associated with the risk of non-liver-related cancers.

Abstract (247 words / 250 words)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Keywords: HCV, HIV co-infection, DAA treatment, mediation analysis, non-liver-related cancers

For Peer Review

INTRODUCTION

Hepatitis C virus (HCV) infection can lead to several liver-related complications (e.g. liver decompensation, hepatocellular carcinoma (HCC), or liver-related death) [1], but also to non-liver-related events such as non-liver-related cancer [2]. Direct-acting antivirals (DAA) allow to achieve a sustained virological response (SVR) in more than 90% of treated participants [3,4]. SVR is associated with a decreased risk of liver and non-liver-related events [4–9]. In a previous study, HIV co-infection was associated with a three-times higher risk of non-liver-related cancer in HCV mono-infected participants after DAA treatment [10]. This could be explained by chronic inflammation and immunosuppression induced by HIV infection [11–14]. HIV co-infection is associated with higher prevalence of alcohol consumption, tobacco consumption [15,16] and metabolic syndrome [17]. These factors have been identified as risk factors for several cancers and could explain the higher risk of non-liver-related cancers observed in HIV co-infected patient [15,18–20]. HIV co-infected patients are also more exposed to oncogenic viruses [21,22]. These viruses are responsible for or are risk factors for several cancers which could explain the higher risk observed in HIV infected patients. The main aim of this study was to estimate the direct effect (reflecting chronic inflammation and immunosuppression), indirect effect (reflecting higher alcohol and tobacco consumptions and metabolic syndrome) and total effect of HIV co-infection on the risk of non-liver-related cancer in HCV infected participants treated with DAA. Sensitivity analyses were carried out to estimate the specific effect of each mediator on the risk of non-liver-related cancers. Finally, to take into account the potential increase of non-liver-related cancers in HIV/HCV co-infected participants due to oncogenic viruses, a sensitivity analysis was carried out focusing on non-liver-related non-oncogenic viruses-related cancers.

METHODS

Patients

HIV/HCV co-infected patients from the ANRS CO13 HEPAVIH cohort (ClinicalTrials.gov Identifier: NCT03324633) and HCV mono-infected patients from the ANRS CO22 HEPATHER cohort (ClinicalTrials.gov Identifier: NCT01953458) were included. Both are multicenter, prospective, nationwide French cohort studies, with follow-up of participants every year with supplementary visits scheduled during anti-HCV treatment. Cirrhotic participants from the ANRS CO13 HEPAVIH cohort had a supplementary visit every six months. Written informed consent was obtained from each participant included in both cohorts. The study followed the ethical principles of the World Medical Association (Declaration of Helsinki) and was approved by an institutional review board (Comité de Protection des Personnes (CPP) Ile de France III, Paris, France – ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER).

The ANRS CO13 HEPAVIH cohort was initiated in 2005 and included HIV/HCV co-infected participants. Due to the development of new anti-HCVs, there were several inclusion periods. The last one, between 2014 and 2016, included participants according to DAA treatment initiation. Whereas, the ANRS CO22 HEPATHER cohort was opened in 2012 and included participants infected by Hepatitis B Virus or HCV.

Participants treated by DAA with or without ribavirin and/or pegylated-interferon between March 1, 2014 and December 31, 2017, not participating in a clinical trial, without history of liver-transplantation or of non-liver-related cancer and with an available SVR status were eligible. For each HIV/HCV co-infected participant, a maximum of 4 HCV mono-infected participants were matched by age at treatment initiation (3 years, more or less) and sex.

Non-liver-related cancer

1
2
3 The primary outcome was time between DAA initiation and the occurrence of a non-
4 liver-related cancer, defined as the occurrence of a cancer which was not an HCC,
5 cholangiocarcinoma or hepato-cholangiocarcinoma. The occurrence of a non-liver-
6 related cancer was declared by investigator centers, with validation by an adjudication
7 committee on medical records. Participants were followed until the occurrence of a
8 non-liver-related cancer, death or the last follow-up visit.
9

10
11
12 For the sensitivity analysis on non-oncogenic virus-related cancers, the occurrence of
13 a cervical uterine cancer, anal cancer, Hodgkin or non-Hodgkin lymphoma or Kaposi
14 sarcoma were considered as competing events.
15

16 **Mediators**

17 All data concerning mediators were measured using a standardized questionnaire
18 during medical follow-up of participants. Data on alcohol and tobacco consumption
19 were collected during participant interviews by a physician. All data were measured at
20 the time of DAA treatment initiation.
21

22
23
24 Even though HIV infection does not induce alcohol or tobacco consumption, the higher
25 rates of these consumptions in HIV co-infected [15,16] could reflect higher risk
26 behaviors in this population. This suggests the need to consider these consumptions
27 as confounding factors. In our population, participants were infected by HIV at
28 baseline. Therefore, the consumptions were measured after HIV infection. The
29 temporality hypothesis needed to define a mediator is thus respected [23]. In addition,
30 due to HIV infection, the reduction of these consumptions is seen as a low priority for
31 both patients and clinicians, leading to lower cessation rates in this population [24–27].
32
33 Indeed, whereas in HCV mono-infected participants the cessation rates are rather high
34 [28], in HIV/HCV co-infected participants the cessation rates are markedly low [25].
35
36 Consequently, although the HIV co-infection did not directly increase the alcohol and
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 tobacco consumption, these consumptions should be considered as mediators in the
4 relationship between HIV co-infection and the risk of non-liver-related cancer
5 (Supplementary Figure 1).
6
7

8 9 10 ***Alcohol consumption***

11 Alcohol consumption was classified into four categories: participants declaring no
12 consumption, consumption between 0 and 20, 20 and 60 and more than 60 grams of
13 alcohol per day. Alcohol consumption in grams per day was estimated by multiplying
14 the number of glasses of alcoholic beverages consumed per day by 10 [29].
15
16
17
18
19

20 21 22 ***Tobacco consumption***

23 Tobacco consumption was classified into four categories: participants declaring no
24 tobacco consumption, consumption between 0 and 15, 15 and 25 and more than 25
25 cigarettes per day.
26
27
28
29

30 31 32 ***Metabolic syndrome***

33 Following the definition of the national cholesterol education program [30], metabolic
34 syndrome was defined by the presence of at least three of the following criteria: high
35 blood pressure, hypertriglyceridemia, reduced HDL-cholesterol, hyperglycemia and
36 obesity. Due to the lack of available data for waist circumference, obesity was defined
37 according to body mass index (BMI) (Table 1).
38
39
40
41
42
43

44 45 46 ***Statistical analysis***

47 Pure direct effect (PDE), total indirect effect (TIE) and total effect (TE) of HIV co-
48 infection on the risk of non-liver-related cancer three years after the initiation of DAA
49 therapy were estimated using mediation analysis [23]. Exposure was HIV co-infection,
50 mediators were alcohol consumption, tobacco consumption and metabolic syndrome
51 and confounding factors were sex, age (in years), HCV transmission routes
52 (intravenous drug use, sexual, transfusion, unknown and others), time since first HCV
53
54
55
56
57
58
59
60

1
2
3 seropositivity (in years), HCV genotype and cirrhosis status defined by cohort specific
4 algorithms previously published [10] taking into account liver biopsy, liver stiffness and
5 non-invasive liver markers (Figure 1). TIE reflected the effect of mediators on the risk
6 of non-liver-related cancers, whereas PDE reflected the effect of chronic inflammation
7 and immunosuppression in the absence of other unmeasured mediators [23].

8
9
10
11
12
13
14 PDE of HIV co-infection (solid pathway) reflects how much the hazard of non-liver-
15 related-cancer at a given time (here, three years) would change if all participants were
16 HIV co-infected versus if none of the participants were HIV co-infected but mediator
17 values were kept at their observed levels. To estimate PDE, first a flexible Cox
18 proportional-hazards model, estimating the baseline hazard with natural cubic splines
19 [31], was fitted to estimate the association between HIV co-infection and the risk of
20 non-liver-cancer adjusted for mediators, age, sex, time since first HCV seropositivity,
21 HCV genotype and cirrhosis. Then, for each HCV mono-infected participants the
22 hazard function λ_{T1,M^0} was estimated by the ratio of the weighted means of survival
23 and density functions if all those participants had been HIV co-infected, but mediator
24 values were kept at their observed levels. The hazard function λ_{T0,M^0} was estimated by
25 the ratio of the weighted means of survival and density functions estimated in the
26 subpopulation of HCV mono-infected patients, and mediator values were kept at their
27 observed values. In the same way, the hazard function λ_{T1M^1} was estimated in the HIV
28 co-infected subpopulation. For each participant, the weight for the estimation of
29 weighted means of survival and density functions was equal to the inverse of the
30 probability that the exposure was at the observed level. The probability was estimated
31 by a logistic model explaining HIV co-infection by confounding factors. PDE was
32 estimated by $\lambda_{T1,M^0} / \lambda_{T0,M^0}$.

33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 TIE of HIV co-infection (dashed pathway) reflects how much the hazard of non-liver-
4 related-cancer would change if exposure was kept at the observed level but mediators
5 values were changed from the level they would have if participants were HIV co-
6 infected versus value they would have if participants were not HIV co-infected. TIE was
7
8 estimated by $\lambda_{T^1, M^1} / \lambda_{T^1, M^0}$.
9
10
11
12
13

14
15 Finally, TE of HIV co-infection reflects how much the hazard of non-liver-related cancer
16 would change if all participants were HIV co-infected versus no participants being HIV
17 co-infected, and mediator values were also changed from the values they would have
18 if none of the participants were HIV co-infected to the values they would have if all
19 participants were HIV co-infected. TE was estimated by multiplying PDE and TIE.
20
21 Confidence intervals at 95% of the effects were estimated using percentile bootstrap.
22
23 Participants with missing data were compared to participants with at least one missing
24 data for variables included in the analysis, according to HIV co-infection. Assuming
25 data were missing at random, missing data for the explanatory variables included in
26 the analysis were imputed by multiple imputation methods using chained equations in
27 R 3.6.2 software using mice package [32]. Ten tables were generated by 10 iterations.
28
29 Quantitative variables were imputed using linear models, while qualitative variables
30 were imputed by logistic or multinomial regression as appropriate. Imputation models
31 included history of non-liver-related cancer or of liver-related event and of anti-HCV
32 treatment, class and duration of DAA treatment, platelet and albumin values, and
33 diabetes, in addition to variables included in the multivariable models for the analysis.
34
35 The normality of the quantitative variables included in the imputation model was
36 graphically checked.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 We carried out several sensitivity analyses. First, only tobacco consumption, and then
4 only alcohol consumption, were considered as mediators. Then, as for the main
5 analysis, we estimated the direct, indirect and total effects of HIV co-infection on the
6 risk of non-liver-related non-oncogenic virus-related cancers.
7
8
9

11 RESULTS

12 Population description

13
14
15 Five-hundred and forty-eight HIV/HCV co-infected and 2016 HCV mono-infected
16 participants were included. Among them, respectively 292 and 1416 had at least a
17 missing data. In HIV/HCV co-infected participants, 164 (39.9%), 154 (28.1%) and 223
18 (40.7%) had missing data respectively for alcohol consumption, tobacco consumption
19 and metabolic syndrome, whereas in HCV mono-infected participants missing data
20 were observed in 679 (33.7%), 64 (3.2%) and 1037 (51.4%), respectively. In HIV co-
21 infected, participants with at least a missing data consumed more alcohol (51.6%
22 declared no alcohol consumption vs 56.6% and 12.5% declared to consumed between
23 20 and 60 grams/day vs 7.0%) and more were cirrhotic (32.3% vs 23.5%) compared
24 to participants without missing data. HCV mono-infected participants with at least a
25 missing data consumed more tobacco (48.1% declared to consumed between 0 and
26 15 cig/day vs 42.2%) and were less frequently with a metabolic syndrome (10.8% vs
27 15.0%) (Supplementary Table 1).
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

47 The median age of the population was 52.9 years [interquartile range (IQR): 49.5; 56.6]
48 and 53.3 years [49.5; 56.9] and 405 (73.9%) and 1478 (73.3%) were men, respectively.
49 HIV co-infected participants were more often infected by HCV due to intravenous drug
50 use (62.2% vs 37.7%), consumed more alcohol (45.1% declared consuming alcohol
51 vs 0.4%), consumed more tobacco (62.9% declared consuming tobacco vs 46.6%)
52 and had a longer time since their first HCV seropositivity (17.9 years [12.1; 22.2] vs
53
54
55
56
57
58
59
60

1
2
3 14.5 years [6.3; 20.8]) but were less frequently cirrhotic (28.1% vs 41.1%) compared
4
5 to HCV mono-infected participants. The proportion of metabolic syndrome (9.2% vs
6
7 13.4%) and SVR rates (93.6% vs 94.5%) were similar between both populations (Table
8
9
10 2).

11 **Risk of non-liver-related cancer**

12
13
14 After a median follow-up of 2.4 years [1.2; 3.3] and 2.9 years [1.7; 3.9], a non-liver-
15
16 related cancer occurred in 22 (of which 17 were non-related to an oncogenic virus) and
17
18 28 (all non-related to an oncogenic virus), respectively, in HIV/HCV co-infected and
19
20 HCV mono-infected participants. Among HIV/HCV co-infected participants, the more
21
22 frequently occurring cancers were: non-melanoma skin (n = 4), anal (n = 2), lung (n =
23
24 2), melanoma (n = 2), nasopharynx (n = 2) and prostate (n = 2) cancers, 2 were AIDS
25
26 defining cancers (1 cervical cancer and 1 non-Hodgkin lymphoma). In HCV mono-
27
28 infected participants, the most observed cancers were non-melanoma skin (n = 5),
29
30 pancreas (n = 5), colon-rectal (n = 3), lung (n = 3), renal-urethra (n = 3) and prostate
31
32 (n = 2) cancers (Supplementary Table 2).

33
34
35
36
37 The TE of HIV co-infection was significantly associated with an increased risk of more
38
39 than three times (HR: 3.7 [1.7; 7.0]) of non-liver-related cancer in HCV mono-infected
40
41 participants. This increased risk in HIV co-infected participants was mainly explained
42
43 by the PDE of HIV co-infection (HR: 3.4 [1.7; 6.6]). In contrast, the TIE of HIV co-
44
45 infection, reflecting the effect of alcohol consumption, tobacco consumption and
46
47 metabolic syndrome, was not significantly associated with the risk of non-liver-related
48
49 cancer (HR: 1.1 [0.8; 1.5]) in HCV infected participants treated by DAA (Fig 2).

50
51
52
53 When considering only tobacco consumption as a potential mediator of the association
54
55 between HIV co-infection and the risk of non-liver-related cancers, similar results were
56
57 found. With PDE, TIE and TE of HIV co-infection on the risk of non-liver-related cancers
58
59
60

1
2
3 were respectively of 3.4 [1.7; 6.6], 1.0 [0.8; 1.3] and 3.5 [1.7; 6.7]. The same results
4
5 were found when considering only alcohol consumption as a potential mediator. PDE,
6
7 TIE and TE estimation were respectively 3.4 [1.7; 6.7], 1.0 [0.7; 1.3] and 3.4 [1.7; 6.7]
8
9 (Table 3).
10

11
12 When excluding oncogenic virus-related cancers, HIV co-infection was still associated
13
14 with a more than three times (HR: 3.1 [1.6; 4.9]) increase in the risk of non-liver-related
15
16 cancers, mainly due to the direct effect of HIV co-infection (HR: 2.4 [1.3; 1.7]) but not
17
18 to the indirect effect of HIV co-infection (HR: 1.3 [0.9; 1.7]) (Table 3).
19

20 21 **DISCUSSION**

22
23 In a population of HCV infected participants treated with DAA followed for up to three
24
25 years after the initiation of the DAA therapy, using a methodology allowing us to
26
27 estimate the direct and indirect effects of an exposure on an outcome, we found that
28
29 HIV co-infection was directly associated with a 3.4-fold increased risk of non-liver-
30
31 related cancer in HCV infected participants. The indirect effect of HIV co-infection,
32
33 reflecting the effects of higher alcohol consumption, tobacco consumption and
34
35 metabolic syndrome, was not significantly associated with the risk of non-liver-related
36
37 cancer in this population. Overall, the total effect of HIV co-infection was associated
38
39 with a 3.7-fold higher risk of non-liver-related cancers in HCV infected participants.
40
41
42
43

44
45 To our knowledge, no other study evaluated the potential impact of HIV co-infection on
46
47 the risk of non-liver-related cancers after DAA treatment in HCV infected participants
48
49 or the potential mediating effect of alcohol consumption, tobacco consumption and
50
51 metabolic syndrome on the relationship between HIV co-infection and risk of non-liver-
52
53 related cancers. Whereas alcohol consumption, tobacco consumption and metabolic
54
55 syndrome are known risk factors for several cancers [15–17], we did not observe here
56
57 a significant mediating effect of these factors for the relationship between HIV co-
58
59
60

1
2
3 infection and the risk of non-liver-related cancer, despite a higher declared alcohol
4 consumption and tobacco consumption in HIV co-infected participants. This could be
5 explained by the very low alcohol and tobacco consumption declared by HCV mono-
6 infected participants, which led to decreased statistical power and did not allow us to
7 perform an analysis with alcohol and tobacco consumption as continuous variables
8 (expressed in grams per day and number of packs per year) rather than categorial
9 variables or to study the direct and indirect effects of HIV co-infection on the risk of
10 each specific cancer. A classification bias due to under-declaration of alcohol and
11 tobacco consumption could also explain why we did not observe a significant TIE in
12 this study. Nevertheless, higher consumption of alcohol and tobacco in HIV co-infected
13 participants has been observed in previous studies [15,16], suggesting that the
14 differences observed in our study for alcohol and tobacco consumption between
15 HIV/HCV co-infected and HCV mono-infected were not due to bias.

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33 This study had several limitations. First, due to the design of the study we included
34 participants from two different cohorts. If data on non-liver-related cancers or on
35 alcohol and tobacco consumption were not collected in the same way in the two
36 cohorts, this could induce misclassification of participants and result in biased
37 estimation of PDE, TIE and TE. However, both cohorts used similar procedures to
38 report all serious adverse events occurring during the follow-up, with extensive data
39 quality controls and monitoring. Moreover, all deaths were adjudicated by a dedicated
40 committee, and consistent checks for non-liver-related cancers were carried out,
41 limiting the risk of differential misclassification. In addition, since the participants came
42 from two different cohorts, this could explain the important differences observed,
43 including on alcohol and tobacco consumption. These differences could have made
44 the two populations incomparable and could explain why we did not observe a
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 significant TIE of HIV co-infection on the risk of non-liver-related cancers. Second,
4 alcohol and tobacco consumption were measured at baseline only. So, we did not take
5
6 into account past consumption or potential cessation before the initiation of DAA. We
7
8 cannot exclude that the difference observed between the two populations for alcohol
9
10 and tobacco consumption was due to higher cessation rates in HCV mono-infected
11
12 than in HIV/HCV co-infected participants. The measurement of consumption at DAA
13
14 treatment initiation may therefore not reflect the differences between the two
15
16 populations concerning lifetime consumption and could explain the absence of a
17
18 significant indirect effect of HIV co-infection on the risk of non-liver-related cancers.
19
20 Third, to estimate the unbiased total, direct and indirect causal effects using mediation
21
22 analysis, some assumptions have to be insured. These assumptions are: no
23
24 unmeasured confounding factors between (1) the exposure and the outcome, (2) the
25
26 mediator and the outcome, (3) the exposure and the mediator and (4) none of the
27
28 mediator-outcome confounders are affected by the exposure. In addition, the direct
29
30 effect of HIV co-infection estimated here reflects the effect of chronic inflammation and
31
32 immunosuppression only if no unmeasured mediators are involved. We identified
33
34 confounding factors of the different studied relations using DAG methodology, and it
35
36 does not appear that we did not take into account some factors. Nevertheless, we
37
38 cannot rule out that some confounding factors were not included in the analysis,
39
40 resulting in bias in the effects estimated. Fourth, the mediation methodology used did
41
42 not allow us to estimate the mediator-specific indirect effect of HIV co-infection [23].
43
44 The estimation of the total indirect effect of HIV co-infection, rather than the indirect
45
46 effects specific to each mediator, could lead to a dilution of the mediating effect if one
47
48 mediator was not associated with the risk of non-liver-related cancer. To take this
49
50 limitation into account, sensitivity analyses were carried out considering only alcohol
51
52
53
54
55
56
57
58
59
60

1
2
3 and tobacco consumption as potential mediators. The results of these sensitivity
4 analyses were similar to those observed in the main analysis. Fifth, the important
5 amount of missing data for mediator values could lead to a selection bias especially if
6 missing data were missing not a random. To reduce this hazard, in addition to variables
7 included in the mediation models, we included in the imputation models factors related
8 to variables with missing values. In addition, missing data were frequent for metabolic
9 syndrome due to its definition, which depends on 5 criteria. To reduce the impact of
10 this definition, we firstly imputed the 5 criteria and then defined the presence of
11 metabolic syndrome for each participant. Finally, due to differences between both
12 populations, notably concerning the mode of transmission of HCV (299 (62.6%) and
13 756 (37.7%) infected due to intravenous drug use, respectively, in HIV/HCV co-
14 infected and HCV mono-infected participants) which could affect the estimation of the
15 direct, indirect and total effects of HIV co-infection on the risk of non-liver-related
16 cancers, it could be more suitable to estimate the effects of HIV infection in the general
17 population.

18
19 This study also had several strengths. First, the large size of the studied population,
20 including 2564 participants who were all treated by DAA. Importantly, the considerable
21 size of the population allows us to have sufficient statistical power. Second, the
22 mediation methodology we used has several advantages, as this approach does not
23 require models for mediators, it allowed us to study non-independent continuous or
24 categorical mediators without needing the rare outcome assumption [23]. Third, both
25 cohorts are prospective French nationwide cohorts with strict monitoring rules allowing
26 for high quality data. Finally, to our knowledge this is the first study estimating the direct
27 and mediating effects of HIV co-infection on the risk of non-liver-related cancers in
28 HCV infected participants treated by DAA.

CONCLUSIONS

In conclusion, in a population of HIV/HCV co-infected participants with controlled HIV viral load, HIV co-infection was associated with a 3.7-fold higher risk of non-liver-related cancers at three years after DAA initiation, compared to HCV mono-infected participants. This increased risk was mainly explained by the direct effect of HIV co-infection, reflecting chronic inflammation and immunosuppression, which was associated with a three-fold increase in the risk of non-liver-related cancers. In contrast, no significant association was observed for the indirect effect of HIV co-infection (reflecting the more frequent alcohol consumption, tobacco consumption and metabolic syndrome) with the risk of non-liver-related cancer.

ACKNOWLEDGMENTS

MC was supported by a doctoral award from the French national Agency for Research on Aids and Viral Hepatitis (ANRS: France Recherche Nord & Sud Sida-HIV Hépatites)

For the ANRS CO13 HEPAVIH cohort study group

Patients of the ANRS CO13 HEPAVIH Cohort

Scientific Committee of the ANRS CO13 HEPAVIH Study Group: D. Salmon (co-Principal investigator), L. Wittkop (co-Principal Investigator & Methodologist), P. Sogni (co-Principal Investigator), L. Esterle (project manager), P. Trimoulet, J. Izopet, L. Serfaty, V. Paradis, B. Spire, P. Carrieri, M.A. Valantin, G. Pialoux, J. Chas, I. Poizot-Martin, K. Barange, A. Naqvi, E. Rosenthal, A. Bicart-See, O. Bouchaud, A. Gervais, C. Lascoux-Combe, C. Goujard, K. Lacombe, C. Duvivier, , D. Neau, P. Morlat, F. Bani-Sadr, L. Meyer, F. Boufassa, , B. Autran, A.M. Roque, C. Solas, H. Fontaine, D. Costagliola, L. Piroth, A. Simon, D. Zucman, F. Boué, P. Mialhes, E. Billaud, H. Aumaître, D. Rey, G. Peytavin, V. Petrov-Sanchez, A. Levier.

Clinical Centres (ward / participating physicians): APHP, Hôpitaux Universitaires Paris Centre, Paris (Médecine Interne et Maladies Infectieuses : D. Salmon, R. Usubillaga; Hépatogastro-entérologie : P. Sogni ; Anatomopathologie : B. Terris ; Virologie :P. Tremeaux) ; APHP Pitié-Salpêtrière, Paris (Maladies Infectieuses et Tropicales : C. Katlama, M.A. Valantin, H. Stitou ; Médecine Interne : A. Simon, P. Cacoub, S. Nafissa ; Hépatogastro-entérologie : Y. Benhamou ; Anatomopathologie : F. Charlotte ; Virologie : S. Fourati) ; APHM Sainte- Marguerite, Marseille (Service d'Immuno-Hématologie Clinique : I. Poizot-Martin, O. Zaegel, H. Laroche ; Virologie : C. Tamalet) ; APHP Tenon, Paris (Maladies Infectieuses et Tropicales : G. Pialoux, J. Chas; Anatomopathologie : P. Callard, F. Bendjaballah ; Virologie : C. Amiel, C. Le Pendeven) ; CHU Purpan, Toulouse (Maladies Infectieuses et Tropicales : B. Marchou

1
2
3 ; Médecine interne : L. Alric ; Hépatogastro-entérologie : K. Barange, S. Metivier ;
4
5 Anatomopathologie : J. Selves ; Virologie : F. Larroquette) ; CHU Archet, Nice
6
7 (Médecine Interne : E. Rosenthal ; Infectiologie : A. Naqvi, V. Rio ; Anatomopathologie
8
9 : J. Haudebourg, M.C. Saint-Paul ; Virologie : A. De Monte, V. Giordanengo, C.
10
11 Partouche) ; APHP Avicenne, Bobigny (Médecine Interne – Unité VIH : O. Bouchaud ;
12
13 Anatomopathologie : A. Martin, M. Zioli ; Virologie : Y. Baazia, V. Iwaka-Bande, A.
14
15 Gerber) ; Hôpital Joseph Ducuing, Toulouse (Médecine Interne : M. Uzan, A. Bicart-
16
17 See, D. Garipuy, M.J. Ferro-Collados ; Anatomopathologie : J. Selves ; Virologie : F.
18
19 Nicot) ; APHP Bichat – Claude-Bernard, Paris (Maladies Infectieuses : A. Gervais, Y.
20
21 Yazdanpanah; Anatomopathologie : H. Adle-Biassette ; Virologie : G. Alexandre,
22
23 Pharmacologie : G. Peytavin) ; APHP Saint-Louis, Paris (Maladies infectieuses : C.
24
25 Lascoux-Combe, J.M. Molina; Anatomopathologie : P. Bertheau; Virologie : M.L.
26
27 Chaix, C. Delaugerre, S. Maylin) ; APHP Saint-Antoine (Maladies Infectieuses et
28
29 Tropicales : K. Lacombe, J. Krause, P.M. Girard, Anatomopathologie : D. Wendum,
30
31 P. Cervera, J. Adam ; Virologie : C. Viala) ; APHP, Hôpitaux Paris Sud, Bicêtre, Paris
32
33 (Maladies Infectieuses et Tropicales : D. Vittecoq ; Médecine Interne : C. Goujard,
34
35 Y. Quertainmont, E. Teicher; Virologie : C. Pallier) ; APHP Necker, Paris (Maladies
36
37 Infectieuses et Tropicales : O. Lortholary, C. Duvivier, C. Rouzaud, J. Lourenco, F.
38
39 Touam, C. Louisin : Virologie : V. Avettand-Fenoel, E. Gardiennet, A. Mélard) ; CHU
40
41 Bordeaux Hôpital Pellegrin, Bordeaux (Maladies Infectieuses et Tropicales : D. Neau,
42
43 A. Ochoa, E. Blanchard, S. Castet-Lafarie, C. Cazanave, D. Malvy, M. Dupon, H.
44
45 Dutronc, F. Dauchy, L. Lacaze-Buzy, A. Desclaux; Anatomopathologie : P. Bioulac-
46
47 Sage ; Virologie : P. Trimoulet, S. Reigadas) ; CHU Bordeaux Hôpital Saint-André,
48
49 Bordeaux (Médecine Interne et Maladies Infectieuses : Médecine Interne et Maladies
50
51 Infectieuses : P. Morlat, D. Lacoste, F. Bonnet, N. Bernard, M. Hessamfar, J. F.
52
53
54
55
56
57
58
59
60

1
2
3 Paccalin, C. Martell, M. C. Pertusa, M. Vandenhende, P. Mercié, D. Malvy, T. Pistone,
4
5 M.C. Receveur, M. Méchain, P. Duffau, C Rivoisy, I. Faure, S. Caldato ; Anatomopathologie : P. Bioulac-Sage ; Virologie : P. Trimoulet, S. Reigadas, P. Bellecave, C.
6
7
8
9
10 Tumiotta) ; CHU Bordeaux Hôpital du Haut-Levêque, Bordeaux (Médecine Interne :
11
12 J.L. Pellegrin, J.F. Viillard, E. Lazzaro, C. Greib ; Anatomopathologie : P. Bioulac-
13
14 Sage ; Virologie : P. Trimoulet, S. Reigadas) ; Hôpital FOCH, Suresnes (Médecine
15
16 Interne : D. Zucman, C. Majerholc ; Virologie : M. Brollo, E. Farfour) ; APHP Antoine
17
18 Béclère, Clamart (Médecine Interne : F. Boué, J. Polo Devoto, I. Kansau, V. Chambrin,
19
20 C. Pignon, L. Berroukeche, R. Fior, V. Martinez, S. Abgrall, M. Favier ; Virologie : C.
21
22 Deback) ; CHU Henri Mondor, Créteil (Immunologie Clinique : Y. Lévy, S. Dominguez,
23
24 J.D. Lelièvre, A.S. Lascaux, G. Melica) ; CHU Nantes Hôpital Hôtel Dieu, Nantes
25
26 (Maladies Infectieuses et Tropicales : E. Billaud, F. Raffi, C. Allavena , V. Reliquet, D.
27
28 Boutoille, C. Biron; M. Lefebvre, N. Hall, S. Bouchez ; Virologie : A. Rodallec, L. Le
29
30 Guen, C. Hemon) ; Hôpital de la Croix Rouse, Lyon (Maladies Infectieuses et
31
32 Tropicales : P. Miaillhes, D. Peyramond, C. Chidiac, F. Ader, F. Biron, A. Boibieux, L.
33
34 Cotte, T. Ferry, T. Perpoint, J. Koffi, F. Zoulim, F. Bailly, P. Lack, M. Maynard, S.
35
36 Radenne, M. Amiri, F Valour ; Hépatogastro-entérologie : J. Koffi, F. Zoulim, F. Bailly,
37
38 P. Lack, M. Maynard, S. Radenne, C. Augustin-Normand ; Virologie : C. Scholtes, T.T.
39
40 Le-Thi) ; CHU Dijon, Dijon (Département d'infectiologie :, L. Piroth, P. Chavanet M.
41
42 Duong Van Huyen, M. Buisson, A. Waldner-Combernoux, S. Mahy, R. Binois, A.L.
43
44 Simonet-Lann, D. Croisier-Bertin, A. Salmon Rousseau, C. Martins) ; CH Perpignan,
45
46 Perpignan (Maladies infectieuses et tropicales : H. Aumaître, Virologie : S. Galim) ;
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Cheneau, M Priester, C Bernard-Henry, E de Mautort, Virologie : P Gantner et S Fafi-
4
5 Kremer)
6
7

8
9 Data collection: F. Roustant, P. Platterier, I. Kmiec, L. Traore, M-K. Youssouf, A.
10
11 Benmammar, M-G. Tateo, S. Lepuil, Pomes ChloéV. Sicart-Payssan, , S.
12
13 Anriamiandrisoa, C. Pomes, F. Touam, C. Louisin, M. Mole, P Catalan, M. Mebarki, A.
14
15 Adda-Lievin, P. Thilbaut, Y. Ousidhoum, F.Z. Makhoukhi, O. Braik, R. Bayoud, C.
16
17 Gatey, M.P. Pietri, V. Le Baut, R. Ben Rayana, F. Barret, C. Chesnel, D. Beniken, M.
18
19 Pauchard, S. Akel, S. Caldato, T. Rojas-Rojas, C. Debreux, L. Chalal, J.Zelie, A. Soria,
20
21 M. Cavellec, S. Breau, P. Fisher, C. Charles, D. Croisier-Bertin, S. Ogoudjobi, C.
22
23
24
25 Brochier, V. Thoirain-Galvan, M. Le Cam.
26
27

28
29 Management, statistical analyses: P. Carrieri, M. Chalouni, V. Conte, L. Dequae-
30
31 Merchadou, M. Desvallees, L. Esterle, C. Gilbert, S. Gillet, R. Knight, T. Lemboub, F.
32
33 Marcellin, L. Michel, M. Mora, C. Protopopescu, P. Roux, B. Spire, S. Tezkratt, T.
34
35 Barré, T. Rojas, M. Baudoin, M. Santos V. Di Beo, M.Nishimwe, , L Wittkop.
36
37

38
39 Funding: ANRS (France Recherche Nord & sud Sida-hiv Hépatites)
40

41
42 **For the ANRS CO22 HEPATHER cohort study group** 
43

44
45 Funding

46
47 ANRS (France REcherche Nord&sud Sida-vih Hepatites), ANR (Agence Nationale de
48
49 la Recherche), DGS (Direction Générale de la Santé) and MSD, Janssen, Gilead,
50
51 Abbvie, BMS, Roche.
52

53
54 ANRS-AFEF Hepather Study group

55
56 Laurent Alric, Delphine Bonnet, Virginie Payssan-Sicart, Chloe Pomes (CHU Purpan,
57
58 Toulouse, France), Fabien Zoulim, François Bailly, Marjolaine Beaudoin, Dominique
59
60

1
2
3 Giboz, Kerstin Hartig-Lavie, Marianne Maynard (Hospices Civils de Lyon, Lyon,
4 France), François Raffi, Eric Billaud, David Boutoille, Morane Cavellec, Marjorie
5 Cheraud-Carpentier (Hôpital Hôtel-Dieu, Nantes, France), Paul Cales, Isabelle Hubert,
6 Pierre Goepfert, Adrien Lannes, Françoise Lunel, Jérôme Boursier (CHU Angers,
7 Angers, France), Tarik Asselah, Nathalie Boyer, Nathalie Giully, Corinne Castelnau,
8 Giovanna Scoazec (Hôpital Beaujon, Clichy, France), Stanislas Pol, Hélène Fontaine,
9 Aziza Chibah, Sylvie Keser, Karim Bonardi, Anaïs Vallet-Pichard, Philippe Sogni
10 (Hôpital Cochin, Paris, France), Victor De Ledinghen, Juliette Foucher, Jean-Baptiste
11 Hiriart, Amandine Legendre, Faiza Chermak, Marie Irlès-Depé (Hôpital Haut-Lévêque,
12 Pessac, Bordeaux, France), Marc Bourlière, Si Nafa Si Ahmed, Christelle Ansaldi,
13 Nisserine Ben Amara, , Valérie Oules, Jacqueline Dunette (Hôpital Saint Joseph,
14 Marseille, France), Albert Tran, Rodolphe Anty, Eve Gelsi, Régine Truchi (CHU de
15 Nice, Nice, France), Dominique Thabut, Elena Luckina, Nadia Messaoudi, Joseph
16 Moussali (Hôpital de la Pitié Salpêtrière, Paris, France), Xavier Causse, Barbara De
17 Dieuleveult, Héloïse Goin, Damien Labarrière, Pascal Potier, Si Nafa Si Ahmed (CHR
18 La Source, Orléans, France), Nathalie Ganne, Véronique Grando-Lemaire, Pierre
19 Nahon, Séverine Brulé, Rym Monard (Hôpital Jean Verdier, Bondy, France),
20 Dominique Guyader, Caroline Jezequel, Audrey Brener, Anne Laligant, Aline Rabot,
21 Isabelle Renard (CHU Rennes, Rennes, France), François Habersetzer, Thomas F.
22 Baumert, Michel Doffoel, Catherine Mutter, Pauline Simo-Noumbissie, Esma Razi
23 (Hôpitaux Universitaires de Strasbourg, Strasbourg, France), Jean-Pierre Bronowicki,
24 Hélène Barraud, Mouni Bensenane, Abdelbasset Nani, Sarah Hassani-Nani, Marie-
25 Albertine Bernard (CHU de Nancy, Nancy, France), Dominique Larrey, Georges-
26 Philippe Pageaux, Michael Bismuth, Ludovic Caillo, Stéphanie Faure, Marie Pierre
27 Ripault (Hôpital Saint Eloi, Montpellier, France), Sophie Métivier, Christophe Bureau,
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Sarah Launay, Jean Marie Peron, Marie Angèle Robic, Léa Tarallo (CHU Purpan,
4
5 Toulouse, France), Thomas Decaens, Marine Faure, Bruno Froissart, Marie-Noelle
6
7 Hilleret, Jean-Pierre Zarski (CHU de Grenoble, Grenoble, France), Ghassan Riachi,
8
9 Odile Gorla, Victorien Grard, Hélène Montialoux (CHU Charles Nicolle, Rouen,
10
11 France), Vincent Leroy, Muriel François, Christian Ouedraogo, Christelle Pauleau,
12
13 Anne Varault (Hôpital Henri Mondor, Créteil, France), Olivier Chazouillères, Tony
14
15 Andreani, Bénédicte Angoulevant, Azeline Chevance, Lawrence Serfaty (Hôpital
16
17 Saint-Antoine, Paris, France), Didier Samuel, Teresa Antonini, Audrey Coilly, Jean-
18
19 Charles Duclos Vallée, Mariagrazia Tateo (Hôpital Paul Brousse, Villejuif, France),
20
21 Armand Abergel, Corinne Bonny, Chanteranne Brigitte, Géraldine Lamblin, Léon Muti
22
23 (Hôpital Estaing, Clermont-Ferrand, France), Claire Geist, Abdenour Babouri, Virginie
24
25 Filipe (Centre Hospitalier Régional, Metz, France), Isabelle Rosa, Camille Barrault,
26
27 Laurent Costes, Hervé Hagège, Soraya Merbah (Centre Hospitalier Intercommunal,
28
29 Créteil, France), Véronique Loustaud-Ratti, Paul Carrier, Maryline Debette-Gratien,
30
31 Jérémie Jacques (CHU Limoges, Limoges, France), Philippe Mathurin, Guillaume
32
33 Lassailly, Florent Artu, Valérie Canva, Sébastien Dharancy, Alexandre Louvet (CHRU
34
35 Claude Huriez, Lille, France), Anne Minello, Marianne Latournerie, Marc Bardou,
36
37 Thomas Mouillot (Dijon University Hospital, Dijon, France), Louis D'Alteroche, Yannick
38
39 Bacq, Didier Barbereau, Charlotte Nicolas (CHU Trousseau, 37044 Tours, France),
40
41 Jérôme Gournay, Caroline Chevalier, Isabelle Archambeaud, Sarah Habes (CHU de
42
43 Nantes, Nantes, France), Isabelle Portal, Nisserine Ben Amara, Danièle Botta-
44
45 Fridlund, (CHU Timone, Marseille, France), Moana Gellu-Simeon, Eric Saillard, Marie-
46
47 Josée Lafrance, (CHU de Pointe-à-Pitre, Pointe-à-Pitre, Guadeloupe).

48
49
50
51
52
53
54
55
56 Scientific Committee:

57
58 - Voting members :

1
2
3 Marc Bourlière (Hôpital St Joseph, Marseille), Jérôme Boursier (CHU Angers, Angers,
4 France), Fabrice Carrat (Scientific Coordinator, Hôpital Saint-Antoine, Paris, France),
5 Patrizia Carrieri (INSERM U912, Marseille, France), Elisabeth Delarocque-Astagneau
6 (Inserm UMR1181, Paris), Victor De Ledinghen (Hôpital Haut-Lévêque, Pessac,
7 Bordeaux, France), Céline Dorival (UPMC & INSERM U1136, Paris, France), Hélène
8 Fontaine (Hôpital Cochin, Paris, France), Slim Fourati (Hôpital Henri Mondor, Créteil,
9 France), Chantal Housset (Inserm UMR-S938 1 IFR65, Paris), Dominique Larrey
10 (Hôpital Saint Eloi, Montpellier, France), Pierre Nahon (Hôpital Jean Verdier, Bondy,
11 France), Georges-Philippe Pageaux (Hôpital Saint Eloi, Montpellier, France),
12 Ventzislava Petrov-Sanchez (ANRS, Paris, France), Stanislas Pol (Principal
13 Investigator, Hôpital Cochin, Paris, France), Sophie Vaux (Agence Nationale de Santé
14 Publique, Saint Maurice, France), Linda Wittkop (ISPED-INSERM U1219, Bordeaux,
15 France), Fabien Zoulim (Hospices Civils de Lyon, Lyon, France), Jessica Zucman-
16 Rossi (Inserm U674/1162, Paris).

17
18
19 - Non voting members:

20
21
22 Marianne L'hennaff (ARCAT-TRT-5-CHV, France), Michèle Sizorn (SOS hépatites,
23 France); one representative of INSERM-ANRS Pharmacovigilance team, Paris,
24 France (Lena Wadouachi, Alpha Diallo), Laure Nailler (INSERM-ANRS, Paris,
25 France), one member of Inserm Transfert, Paris, France (Alice Bousselet, Mireille
26 Caralp), and one representative of each pharmaceutical company (MSD, Gilead,
27 Abbvie).

28
29
30 Sponsor: Alpha Diallo, Laura Nailler, Lena Wadouachi (INSERM-ANRS, Paris,
31 France), Ventzi Petrov-Sanchez (coordinator).

32
33
34 Methodology and Coordinating Centre: Douae Ammour, Loubna Ayour, Jaouad
35 Benhida, Fabrice Carrat (coordinator), Frederic Chau, Céline Dorival, Isabelle Goderel,
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Warda Hadi, Clovis Lusivika-Nzinga, Grégory Pannetier, François Pinot, Odile Stahl,
4
5 François Téloulé (Sorbonne Université & INSERM U1136, Paris, France).
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

REFERENCES

1. Westbrook RH, Dusheiko G. Natural history of hepatitis C. *J Hepatol*. 2014 Nov;61(1 Suppl):S58-68.
2. Allison RD, Tong X, Moorman AC, Ly KN, Rupp L, Xu F, et al. Incidence of Cancer and Cancer-related Mortality Among Persons with Chronic Hepatitis C Infection, 2006–2010. *J Hepatol*. 2015 Oct;63(4):822–8.
3. Naggie S, Cooper C, Saag M, Workowski K, Ruane P, Towner WJ, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med*. 2015 Aug 20;373(8):705–13.
4. Bang CS, Song IH. Impact of antiviral therapy on hepatocellular carcinoma and mortality in patients with chronic hepatitis C: systematic review and meta-analysis. *BMC Gastroenterol*. 2017 Apr 4;17(1):46.
5. Nahon P, Bourcier V, Layese R, Audureau E, Cagnot C, Marcellin P, et al. Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications. *Gastroenterology*. 2017 Jan;152(1):142-156.e2.
6. Chew KW, Hua L, Bhattacharya D, Butt AA, Bornfleth L, Chung RT, et al. The effect of hepatitis C virologic clearance on cardiovascular disease biomarkers in human immunodeficiency virus/hepatitis C virus coinfection. *Open Forum Infect Dis*. 2014 Dec;1(3):ofu104.
7. Tada T, Kumada T, Toyoda H, Kiriya S, Tanikawa M, Hisanaga Y, et al. Viral eradication reduces all-cause mortality, including non-liver-related disease, in patients with progressive hepatitis C virus-related fibrosis. *J Gastroenterol Hepatol*. 2017 Mar;32(3):687–94.
8. Bruno S, Di Marco V, Iavarone M, Roffi L, Boccaccio V, Crosignani A, et al. Improved survival of patients with hepatocellular carcinoma and compensated

1
2
3 hepatitis C virus-related cirrhosis who attained sustained virological response. *Liver Int*
4
5 *Off J Int Assoc Study Liver*. 2017 Apr 18;

6
7
8 9. Carrat F, Fontaine H, Dorival C, Simony M, Diallo A, Hezode C, et al. Clinical
9
10 outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a
11
12 prospective cohort study. *Lancet Lond Engl*. 2019 Apr 6;393(10179):1453–64.

13
14
15 10. Chalouni M, Pol S, Sogni P, Fontaine H, Lacombe K, Lacombe JM, et al.
16
17 Increased mortality in HIV/HCV-coinfected compared to HCV-monoinfected patients in
18
19 the DAA era due to non-liver-related death. *J Hepatol*. 2020 Aug 13;

20
21
22 11. Franzetti M, Ricci E, Bonfanti P. The Pattern of Non-AIDS-defining Cancers in
23
24 the HIV Population: Epidemiology, Risk Factors and Prognosis. A Review. *Curr HIV*
25
26 *Res*. 2019;17(1):1–12.

27
28
29 12. Franzetti M, Adorni F, Parravicini C, Vergani B, Antinori S, Milazzo L, et al.
30
31 Trends and predictors of non-AIDS-defining cancers in men and women with HIV
32
33 infection: a single-institution retrospective study before and after the introduction of
34
35 HAART. *J Acquir Immune Defic Syndr* 1999. 2013 Apr 1;62(4):414–20.

36
37
38 13. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in
39
40 people with HIV/AIDS compared with immunosuppressed transplant recipients: a
41
42 meta-analysis. *Lancet Lond Engl*. 2007 Jul 7;370(9581):59–67.

43
44
45 14. Tien PC, Choi AI, Zolopa AR, Benson C, Tracy R, Scherzer R, et al.
46
47 Inflammation and mortality in HIV-infected adults: analysis of the FRAM study cohort.
48
49 *J Acquir Immune Defic Syndr* 1999. 2010 Nov;55(3):316–22.

50
51
52 15. Silverberg MJ, Chao C, Leyden WA, Xu L, Tang B, Horberg MA, et al. HIV
53
54 infection and the risk of cancers with and without a known infectious cause. *AIDS Lond*
55
56 *Engl*. 2009 Nov 13;23(17):2337–45.

57
58
59 16. Santos ME, Protopopescu C, Sogni P, Yaya I, Piroth L, Bailly F, et al. HCV-

1
2
3 Related Mortality Among HIV/HCV Co-infected Patients: The Importance of Behaviors
4 in the HCV Cure Era (ANRS CO13 HEPAVIH Cohort). *AIDS Behav.* 2020
5
6 Apr;24(4):1069–84.

7
8
9
10 17. Krishnan S, Schouten JT, Atkinson B, Brown T, Wohl D, McComsey GA, et al.
11 Metabolic syndrome before and after initiation of antiretroviral therapy in treatment-
12 naive HIV-infected individuals. *J Acquir Immune Defic Syndr* 1999. 2012 Nov
13
14 1;61(3):381–9.

15
16
17
18 18. Choi YJ, Lee DH, Han K-D, Shin CM, Kim N. Abdominal obesity, glucose
19 intolerance and decreased high-density lipoprotein cholesterol as components of the
20
21 metabolic syndrome are associated with the development of colorectal cancer. *Eur J*
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

18. Choi YJ, Lee DH, Han K-D, Shin CM, Kim N. Abdominal obesity, glucose intolerance and decreased high-density lipoprotein cholesterol as components of the metabolic syndrome are associated with the development of colorectal cancer. *Eur J Epidemiol.* 2018 Nov;33(11):1077–85.

19. Gathirua-Mwangi WG, Song Y, Monahan PO, Champion VL, Zollinger TW. Associations of metabolic syndrome and C-reactive protein with mortality from total cancer, obesity-linked cancers and breast cancer among women in NHANES III. *Int J Cancer.* 2018 01;143(3):535–42.

20. Gacci M, Russo GI, De Nunzio C, Sebastianelli A, Salvi M, Vignozzi L, et al. Meta-analysis of metabolic syndrome and prostate cancer. *Prostate Cancer Prostatic Dis.* 2017;20(2):146–55.

21. Humans IWG on the E of CR to. Biological Agents. International Agency for Research on Cancer; 2012.

22. de Martel C, Shiels MS, Franceschi S, Simard EP, Vignat J, Hall HI, et al. Cancers attributable to infections among adults with HIV in the United States. *AIDS Lond Engl.* 2015 Oct 23;29(16):2173–81.

23. Fasanelli F, Giraudo MT, Ricceri F, Valeri L, Zugna D. Marginal Time-Dependent Causal Effects in Mediation Analysis With Survival Data. *Am J Epidemiol.*

1
2
3 2019 01;188(5):967–74.
4

5 24. Fredericksen R, Edwards T, Crane HM, Crane PK, Merlin J, Gibbons LE, et al.
6 Patient and provider priorities for self-reported domains of HIV clinical care. *AIDS Care*.
7 2015 Oct;27(10):1255–64.
8
9

10 25. Strauss SM, Tiburcio NJ, Munoz-Plaza C, Gwadz M, Luniewicz J, Osborne A, et
11 al. HIV care providers' implementation of routine alcohol reduction support for their
12 patients. *AIDS Patient Care STDs*. 2009 Mar;23(3):211–8.
13
14

15 26. Pacek LR, McClernon FJ, Bosworth HB. Adherence to Pharmacological
16 Smoking Cessation Interventions: A Literature Review and Synthesis of Correlates and
17 Barriers. *Nicotine Tob Res*. 2018 Oct;20(10):1163–72.
18
19

20 27. Shahrir S, Crothers K, McGinnis KA, Chan KCG, Baeten JM, Wilson SM, et al.
21 Receipt and predictors of smoking cessation pharmacotherapy among veterans with
22 and without HIV. *Prog Cardiovasc Dis*. 2020 Mar 1;63(2):118–24.
23
24

25 28. Proeschold-Bell RJ, Evon DM, Yao J, Niedzwiecki D, Makarushka C, Keefe KA,
26 et al. A Randomized Controlled Trial of an Integrated Alcohol Reduction Intervention
27 in Patients With Hepatitis C Infection. *Hepatology*. 2020 Jun;71(6):1894–909.
28
29

30 29. Kalinowski A, Humphreys K. Governmental standard drink definitions and low-
31 risk alcohol consumption guidelines in 37 countries. *Addiction*. 2016;111(7):1293–8.
32
33

34 30. Expert Panel on Detection, Evaluation, and Treatment of High Blood
35 Cholesterol in Adults. Executive Summary of The Third Report of The National
36 Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And
37 Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001
38 May 16;285(19):2486–97.
39
40

41 31. Royston P, Parmar MKB. Flexible parametric proportional-hazards and
42 proportional-odds models for censored survival data, with application to prognostic
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 modelling and estimation of treatment effects. Stat Med. 2002 Aug 15;21(15):2175–
4
5 97.

6
7 32. Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by
8
9 Chained Equations in R. J Stat Softw. 2011 Dec 12;45(1):1–67.
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

TABLES**Table 1.** Risk factors and levels for defining a metabolic syndrome following the national cholesterol education program recommendations

Risk factor	Level
High blood pressure	
Systolic blood pressure	≥ 130 mmHg
Diastolic blood pressure	≥ 85 mmHg
Hypertriglyceridemia	≥ 150 mg/dl
Reduced HDL-cholesterol	
<i>Men</i>	≤ 40 mg/dl
<i>Women</i>	≤ 50 mg/dl
Hyperglycemia	≥ 100 mg/dl
Obesity	≥ 30 kg/m ²

Table 2. Description of Hepatitis C Virus infected participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts at the time of Direct-Acting Antivirals treatment initiation according to HIV co-infection

Characteristics	HIV [†] /HCV [‡] co-infected (<i>n</i> = 548)		HCV [‡] mono-infected (<i>n</i> = 2016)	
	<i>n</i>	Median [IQR [§]] or <i>n</i> (%)	<i>n</i>	Median [IQR [§]] or <i>n</i> (%)
Age (years)	548	52.9 [49.5; 56.6]	2016	53.2 [49.5; 56.9]
Men	548	405 (73.9%)	2016	1478 (73.3%)
HCV [‡] transmission routes	481		2004	
Injecting drug use		299 (62.2%)		756 (37.7%)
Sexual		85 (17.7%)		21 (1.0%)
Transfusion		37 (7.7%)		465 (23.2%)
Unknown		55 (11.4%)		459 (22.9%)
Other		5 (1.0%)		303 (15.1%)
Time since first HCV [‡] seropositivity (years)	522	17.9 [12.1; 22.2]	2016	14.4 [6.3; 20.8]
Cirrhosis	512	144 (28.1%)	1896	779 (41.1%)
Current alcohol consumption (gram/day)	384	0.0 [0.0; 5.7]	1337	0.0 [0.0; 0.0]
0		211 (54.9%)		1330 (99.5%)
]0 ; 20]		133 (34.6%)		3 (0.2%)
]20 ; 60]		34 (8.9%)		1 (0.1%)
> 60		6 (1.6%)		3 (0.2%)
Current tobacco consumption (cig/year)	394	7.0 [0.0; 20.0]	1952	0.0 [0.0; 1.0]
0		149 (37.8%)		1048 (53.3%)
]0 ; 15]		136 (34.5%)		903 (46.3%)
]15 ; 25]		75 (19.0%)		1 (0.1%)
> 25		34 (8.6%)		0 (0.0%)
Metabolic syndrome	325	30 (9.2%)	979	131 (13.4%)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

CD4 count (in cells/mm³)	543	622 [431; 864.5]	-	-
< 200		31 (5.7%)		
[200 ; 500[156 (28.7%)		
≥ 500		356 (65.6%)		
Detectable HIV[†] viral load	520	68 (13.1%)		

[†]Human Immunodeficiency virus, [‡]Hepatitis C virus, [§]Interquartile Range

For Peer Review

Table 3. HIV co-infection direct, indirect, and total effects on the risk of non-liver-related cancer and non-liver-related non-oncogenic virus-related cancers at three years after the initiation of Direct-Acting Antivirals treatment in Hepatitis C Virus infected participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts

Effects	HR [†]	95% CI [‡]
Current tobacco consumption as only mediator		
<i>Pure direct effect (PDE)</i>	3.4	[1.7; 6.6]
<i>Total indirect effect (TIE)</i>	1.0	[0.8; 1.3]
<i>Total effect (TE)</i>	3.5	[1.7; 6.7]
Current alcohol consumption as only mediator		
<i>Pure direct effect</i>	3.4	[1.7; 6.5]
<i>Total indirect effect</i>	1.0	[0.7; 1.3]
<i>Total effect</i>	3.4	[1.7; 6.7]
Non-liver-related non-oncogenic virus-related cancers		
<i>Pure direct effect</i>	2.4	[1.2; 5.0]
<i>Total indirect effect</i>	1.3	[0.9; 1.7]
<i>Total effect</i>	3.1	[1.6; 4.9]

[†] HR: Hazard Ratio

[‡] CI 95%: Confidence interval at 95%

FIGURE LEGENDS

Figure 1. Assumed causal relationship between HIV co-infection in Hepatitis C Virus infected patients, alcohol consumption, tobacco consumption, metabolic syndrome and non-liver-related cancer

Figure 2. Direct, indirect and total effects of HIV co-infection on the risk of non-liver-related cancers in participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts

For Peer Review

CONFLICT OF INTEREST STATEMENT

Source of supports:

This work was supported by the French national Agency for Research on Aids and Viral Hepatitis (ANRS: France Recherche Nord & Sud Sida-HIV Hépatites)

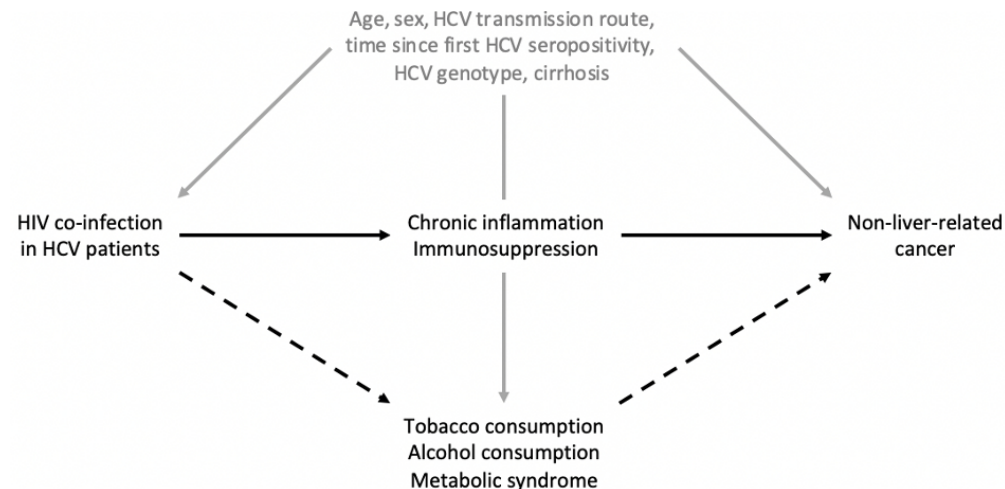
Conflicts of Interest and Source of Funding:

Dr S Pol has received consulting and lecturing fees from Bristol-Myers Squibb, Janssen, Gilead, Roche, MSD and Abbvie, Biotest, Shinogi, ViiV and grants from Bristol-Myers Squibb, Gilead, Roche and MSD

Dr P Sogni has received consulting and lecturing fees from AbbVie, Genfit, Gilead, Janssen, Mayoly-Spindler, MSD

Dr H. Fontaine has lecturing fees from Abbvie Gilead and MSD

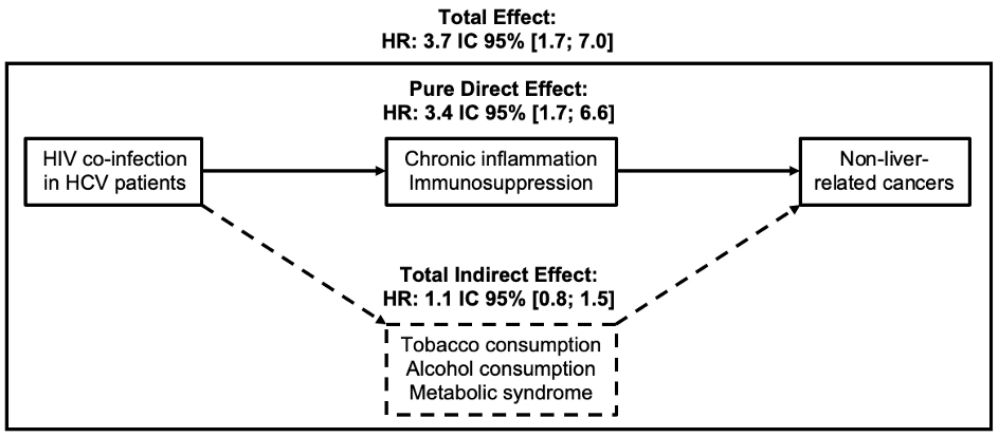
Dr D. Salmon has lecturing fees from Abbvie and Gilead



Assumed causal relationship between HIV co-infection in Hepatitis C Virus infected patients, alcohol consumption, tobacco consumption, metabolic syndrome and non-liver-related cancer

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Direct, indirect and total effects of HIV co-infection on the risk of non-liver-related cancers in participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts