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

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Running head: HIV co-infection effects on cancers risk

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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)

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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

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

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

Mediators

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

Even though HIV infection does not induce alcohol or tobacco consumption, the higher rates of these consumptions in HIV co-infected [15,16] could reflect higher risk behaviors in this population. This suggests the need to consider these consumptions as confounding factors. In our population, participants were infected by HIV at baseline. Therefore, the consumptions were measured after HIV infection. The temporality hypothesis needed to define a mediator is thus respected [23]. In addition, due to HIV infection, the reduction of these consumptions is seen as a low priority for both patients and clinicians, leading to lower cessation rates in this population [24–27]. Indeed, whereas in HCV mono-infected participants the cessation rates are rather high [28], in HIV/HCV co-infected participants the cessation rates are markedly low [25]. Consequently, although the HIV co-infection did not directly increase the alcohol and

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

Alcohol consumption

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

Tobacco consumption

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

Metabolic syndrome

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

Statistical analysis

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

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

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

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

Finally, TE of HIV co-infection reflects how much the hazard of non-liver-related cancer would change if all participants were HIV co-infected versus no participants being HIV co-infected, and mediator values were also changed from the values they would have if none of the participants were HIV co-infected to the values they would have if all participants were HIV co-infected. TE was estimated by multiplying PDE and TIE. Confidence intervals at 95% of the effects were estimated using percentile bootstrap. Participants with missing data were compared to participants with at least one missing data for variables included in the analysis, according to HIV co-infection. Assuming data were missing at random, missing data for the explanatory variables included in the analysis were imputed by multiple imputation methods using chained equations in R 3.6.2 software using mice package [32]. Ten tables were generated by 10 iterations. Quantitative variables were imputed using linear models, while qualitative variables were imputed by logistic or multinomial regression as appropriate. Imputation models included history of non-liver-related cancer or of liver-related event and of anti-HCV treatment, class and duration of DAA treatment, platelet and albumin values, and diabetes, in addition to variables included in the multivariable models for the analysis. The normality of the quantitative variables included in the imputation model was graphically checked.

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

RESULTS

Population description

Five-hundred and forty-eight HIV/HCV co-infected and 2016 HCV mono-infected participants were included. Among them, respectively 292 and 1416 had at least a missing data. In HIV/HCV co-infected participants, 164 (39.9%), 154 (28.1%) and 223 (40.7%) had missing data respectively for alcohol consumption, tobacco consumption and metabolic syndrome, whereas in HCV mono-infected participants missing data were observed in 679 (33.7%), 64 (3.2%) and 1037 (51.4%), respectively. In HIV co-infected, participants with at least a missing data consumed more alcohol (51.6% declared no alcohol consumption *vs* 56.6% and 12.5% declared to consumed between 20 and 60 grams/day *vs* 7.0%) and more were cirrhotic (32.3% *vs* 23.5%) compared to participants without missing data. HCV mono-infected participants with at least a missing data consumed more tobacco (48.1% declared to consumed between 0 and 15 cig/day *vs* 42.2%) and were less frequently with a metabolic syndrome (10.8% *vs* 15.0%) (Supplementary Table 1).

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

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

Risk of non-liver-related cancer

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

The TE of HIV co-infection was significantly associated with an increased risk of more than three times (HR: 3.7 [1.7; 7.0]) of non-liver-related cancer in HCV mono-infected participants. This increased risk in HIV co-infected participants was mainly explained by the PDE of HIV co-infection (HR: 3.4 [1.7; 6.6]). In contrast, the TIE of HIV co-infection, reflecting the effect of alcohol consumption, tobacco consumption and metabolic syndrome, was not significantly associated with the risk of non-liver-related cancer (HR: 1.1 [0.8; 1.5]) in HCV infected participants treated by DAA (Fig 2).

When considering only tobacco consumption as a potential mediator of the association between HIV co-infection and the risk of non-liver-related cancers, similar results were found. With PDE, TIE and TE of HIV co-infection on the risk of non-liver-related cancers

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 were found when considering only alcohol consumption as a potential mediator. PDE, 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] (Table 3).

When excluding oncogenic virus-related cancers, HIV co-infection was still associated with a more than three times (HR: 3.1 [1,6; 4.9]) increase in the risk of non-liver-related cancers, mainly due to the direct effect of HIV co-infection (HR: 2.4 [1.3; 1.7]) but not to the indirect effect of HIV co-infection (HR: 1.3 [0.9; 1.7]) (Table 3).

DISCUSSION

In a population of HCV infected participants treated with DAA followed for up to three years after the initiation of the DAA therapy, using a methodology allowing us to estimate the direct and indirect effects of an exposure on an outcome, we found that HIV co-infection was directly associated with a 3.4-fold increased risk of non-liver-related cancer in HCV infected participants. The indirect effect of HIV co-infection, reflecting the effects of higher alcohol consumption, tobacco consumption and metabolic syndrome, was not significantly associated with the risk of non-liver-related cancer in this population. Overall, the total effect of HIV co-infection was associated with a 3.7-fold higher risk of non-liver-related cancers in HCV infected participants.

To our knowledge, no other study evaluated the potential impact of HIV co-infection on the risk of non-liver-related cancers after DAA treatment in HCV infected participants or the potential mediating effect of alcohol consumption, tobacco consumption and metabolic syndrome on the relationship between HIV co-infection and risk of non-liver-related cancers. Whereas alcohol consumption, tobacco consumption and metabolic syndrome are known risk factors for several cancers [15–17], we did not observe here a significant mediating effect of these factors for the relationship between HIV co-

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

This study had several limitations. First, due to the design of the study we included participants from two different cohorts. If data on non-liver-related cancers or on alcohol and tobacco consumption were not collected in the same way in the two cohorts, this could induce misclassification of participants and result in biased estimation of PDE, TIE and TE. However, both cohorts used similar procedures to report all serious adverse events occurring during the follow-up, with extensive data quality controls and monitoring. Moreover, all deaths were adjudicated by a dedicated committee, and consistent checks for non-liver-related cancers were carried out, limiting the risk of differential misclassification. In addition, since the participants came from two different cohorts, this could explain the important differences observed, including on alcohol and tobacco consumption. These differences could have made the two populations incomparable and could explain why we did not observe a

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significant TIE of HIV co-infection on the risk of non-liver-related cancers. Second, alcohol and tobacco consumption were measured at baseline only. So, we did not take into account past consumption or potential cessation before the initiation of DAA. We cannot exclude that the difference observed between the two populations for alcohol and tobacco consumption was due to higher cessation rates in HCV mono-infected than in HIV/HCV co-infected participants. The measurement of consumption at DAA treatment initiation may therefore not reflect the differences between the two populations concerning lifetime consumption and could explain the absence of a significant indirect effect of HIV co-infection on the risk of non-liver-related cancers. Third, to estimate the unbiased total, direct and indirect causal effects using mediation analysis, some assumptions have to be insured. These assumptions are: no unmeasured confounding factors between (1) the exposure and the outcome, (2) the mediator and the outcome, (3) the exposure and the mediator and (4) none of the mediator-outcome confounders are affected by the exposure. In addition, the direct effect of HIV co-infection estimated here reflects the effect of chronic inflammation and immunosuppression only if no unmeasured mediators are involved. We identified confounding factors of the different studied relations using DAG methodology, and it does not appear that we did not take into account some factors. Nevertheless, we cannot rule out that some confounding factors were not included in the analysis, resulting in bias in the effects estimated. Fourth, the mediation methodology used did not allow us to estimate the mediator-specific indirect effect of HIV co-infection [23]. The estimation of the total indirect effect of HIV co-infection, rather than the indirect effects specific to each mediator, could lead to a dilution of the mediating effect if one mediator was not associated with the risk of non-liver-related cancer. To take this limitation into account, sensitivity analyses were carried out considering only alcohol

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

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

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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, Kiriyama 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

hepatitis C virus-related cirrhosis who attained sustained virological response. Liver Int Off J Int Assoc Study Liver. 2017 Apr 18;

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

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

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

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

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

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

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

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

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

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

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.

2019 01;188(5):967–74.

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

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

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

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

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

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

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

31.   Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic

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

32.   Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011 Dec 12;45(1):1–67.

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	
Men	≤ 40 mg/dl
Women	≤ 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 *(n = 548)*		HCV[‡] mono-infected *(n = 2016)*	
	n	Median [IQR[§]] or n (%)	n	Median [IQR[§]] or n (%)
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%)

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CD4 count (*in cells/mm^3***)**	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%)		

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

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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		
Pure direct effect (PDE)	3.4	[1.7; 6.6]
Total indirect effect (TIE)	1.0	[0.8; 1.3]
Total effect (TE)	3.5	[1.7; 6.7]
Current alcohol consumption as only mediator		
Pure direct effect	3.4	[1.7; 6.5]
Total indirect effect	1.0	[0.7; 1.3]
Total effect	3.4	[1.7; 6.7]
Non-liver-related non-oncogenic virus-related cancers		
Pure direct effect	2.4	[1.2; 5.0]
Total indirect effect	1.3	[0.9; 1.7]
Total effect	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

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CONFLICT OF INTEREST STATEMENT

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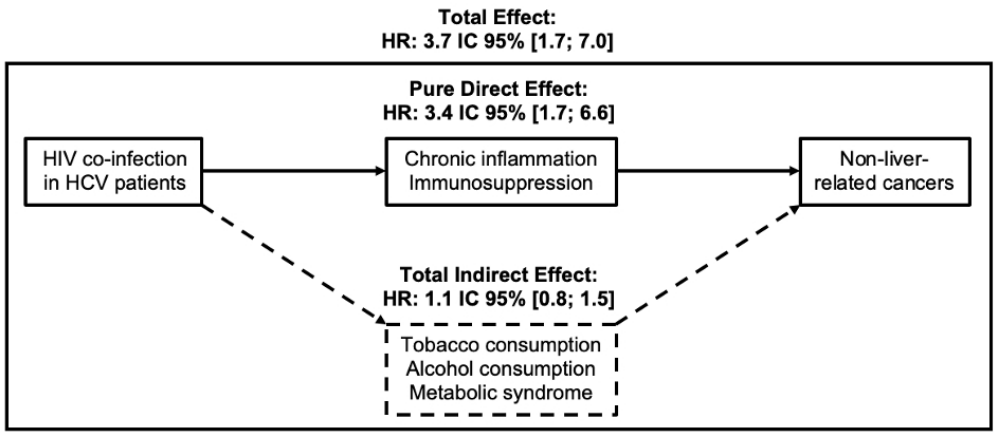Dr H. Fontaine has lecturing fees from Abbvie Gilead and MSD

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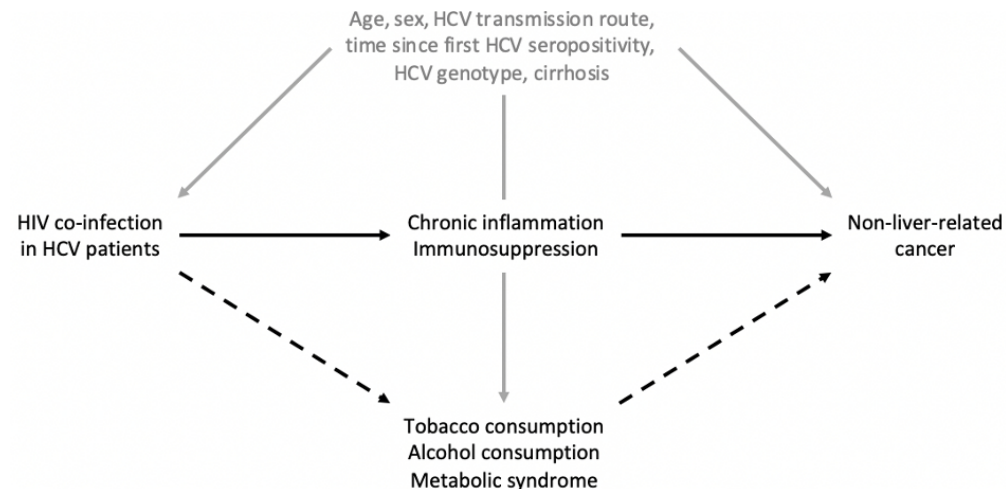
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Assumed causal relationship between HIV co-infection in Hepatitis C Virus infected patients, alcohol consumption, tobacco consumption, metabolic syndrome and non-liver-related cancer

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Total Effect:
HR: 3.7 IC 95% [1.7; 7.0]

Pure Direct Effect:
HR: 3.4 IC 95% [1.7; 6.6]

| HIV co-infection in HCV patients | → | Chronic inflammation Immunosuppression | → | Non-liver-related cancers |

Total Indirect Effect:
HR: 1.1 IC 95% [0.8; 1.5]

Tobacco consumption
Alcohol consumption
Metabolic syndrome

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