HIV CO-INFECTION AND RISK OF MORBIDITY AND MORTALITY IN HCV PATIENTS TREATED BY DAA

M. CHALOUNI[1], S. POL[2-3], P. SOGNI[4-5], H. FONTAINE[2], K. LACOMBE[6-7], JM. LACOMBE[8], L. ESTERLE[1], C. GILBERT[1], C. DORIVAL[6], D. SALMON[4-9], F. CARRAT[6-10]*, L. WITTKOP[1-11]* for the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts study group

* equal contribution, [1]Univ. Bordeaux, ISPED, Inserm, Bordeaux Population Health Research Center, team MORPH3EUS, UMR 1219, CIC-EC 1401, F-33000 Bordeaux, France, [2]AP-HP, Hôpital Cochin, Unité d'Hépatologie, Paris, France, [3]Université Paris Descartes, INSERM U1223 and USM-20, Institut Pasteur, Paris, France, [4]Université Paris Descartes, Paris, France, [5]INSERM U1223, Institut Pasteur, Paris, France, [6]Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, IPLESP, F75012, Paris, France, [7]APHP, Hôpital Saint-Antoine, Service de Maladies Infectieuses et Tropicales, Paris, F75012, France, [8]INSERM Transfert, Paris, France, [9]Service Maladies infectieuses et tropicales, AP-HP, Hôpital Cochin, Paris, France, [10]AP-HP, Hôpital Saint-Antoine, Unité de Santé Publique, Paris, France, [11]CHU de Bordeaux, Pôle de santé publique, F-33000 Bordeaux, France

CONTEXT

- **HIV co-infection** leads to **increased mortality**, **liver disease progression** and **extra-hepatic manifestations** in **HCV-infected** patients.
- **DAA** lead to **high SVR rates** and **decrease the risk of disease progression** both in **HCV mono-infected** and **HIV/HCV co-infected** participants.
- **Disease evolution after DAA** treatment in **HIV/HCV** co-infected **compared to HCV** mono-infected patients has **rarely been studied**.

Objectives:

- To compare risks of liver-related events, liver-related mortality and non-liver-related mortality in HIV/HCV co-infected and HCV mono-infected participants treated by DAA using data from two large French nationwide cohort studies.

METHODS

Population: Participants from the ANRS CO13 HEPAVIH cohort (HIV/HCV) and from the ANRS CO22 HEPATHER cohort (HCV) were included if they:

- Initiated a **DAA** treatment between **March 2014** and **December 2017**.
- Treated **outside a clinical trial**.
- **Without history of liver transplantation**.
- With an **available SVR** status.

- **Up to 4 HCV mono-infected** participants were **matched to each HIV/HCV co-infected** participants on **age** (+/- 3 years) and **sex**.

Baseline: Date of **DAA** treatment **initiation**.

Follow-up: **Follow-up ended** at time of **liver-related event**, **death** or **last follow-up**.

Outcomes:

- **Liver-related events:**
  - **Liver decompensation** (liver encephalopathy, hepatorenal syndrome, esophageal varices bleeding, ascites and jaundice)
  - **Hepatocellular carcinoma** (HCC)
  - **Liver transplantation**
  - **Liver-related death**
- **Liver-related mortality:** Death due to HCV
- **Non-liver-related mortality:** Death due to any cause other than HCV

Statistical analysis:

- Cox proportional hazards models adjusted on age, sex, time since first HCV seropositivity, HCV contamination route, HCV genotype, cirrhosis, SVR (as a time dependent variable), alcohol and tobacco consumption.
- Assuming data were **missing at random** we realized **multiple imputation.**
- **Predicted events probabilities over time** were estimated for **mean participants according to HIV co-infection** using Cox models linear predictors.

RESULTS

Population: 592 HIV/HCV co-infected and **2049 HCV** mono-infected participants were included

SVR rates were of **92.9%** in **HIV/HCV** co-infected and **94.6%** in **HCV** mono-infected participants.

Table 1. Characteristics at time of DAA initiation according to HIV co-infection in HCV infected participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts

	HIV§/HCV* co-infected *(n = 592)*	HCV* mono-infected *(n = 2049)*
Characteristics	**Median [IQR¥] or n (%)**	**Median [IQR¥] or n (%)**
Age *(years)*$^{\psi}$	52.9 [49.6 ; 56.7]	53.3 [49.6 ; 56.9]
Men$^{\psi}$	436 (73.6%)	1498 (73.1%)
BMI$^{\Delta}$ (kg/m^2)	22.7 [20.2 ; 25.3]	24.7 [22.3 ; 27.5]
Alcohol consumption$^{\psi}$		
Never	134 (23.1%)	832 (60.5%)
Past	137 (23.6%)	514 (37.4%)
Current	310 (53.4%)	29 (2.1%)
Tobacco consumption$^{\psi}$		
Never	98 (17.0%)	504 (24.6%)
Past	130 (22.5%)	550 (26.9%)
Current	350 (60.6%)	991 (48.5%)
Time since first HCV* seropositivity *(years)*$^{\psi}$	18.0 [12.4 ; 22.2]	14.5 [6.4 ; 20.8]
HCV* contamination route$^{\psi}$		
Drug Use	325 (62.5%)	765 (37.6%)
Sexual	92 (17.7%)	21 (1.0%)
Transfusion	40 (7.7%)	476 (23.4%)
Unknown	57 (11.0%)	465 (22.8%)
Other	6 (1.2%)	310 (15.2%)
HCV* genotype$^{\psi}$		
1	313 (53.7%)	1293 (63.6%)
2	22 (3.8%)	80 (3.9%)
3	85 (14.6%)	334 (16.4%)
4	160 (27.4%)	306 (15.0%)
5/6/7	3 (0.5%)	21 (1.0%)
Cirrhosis$^{\psi}$	159 (28.8%)	793 (41.2%)
ARV$^{\text{¤}}$ **intake**	577 (97.5%)	-
CD4 count *(cells/mm^3)*	614.0 [411.0 ; 861.0]	-
Undetectable HIV§ viral load	488 (86.8%)	-

§ Human immunodeficiency virus, * Hepatitis C virus, ¥ Interquartile range, $^{\Delta}$ Body mass index, ¤ Antiretroviral
$^{\psi}$ Adjustment variables

Outcomes after DAA initiation:

- **Liver-related events:**
  - **17** (5 HCC, 8 liver decompensations, 4 liver-related deaths) in **HIV/HCV**
  - **66** (55 HCC, 10 liver decompensations, 1 liver-related death) in **HCV**
- **Liver-related mortality:**
  - **8** (5 HCC, 2 liver decompensations, 1 liver transplantation) in **HIV/HCV**
  - **28** (15 HCC, 9 liver decompensations, 2 liver transplantations, 2 cholangiocarcinoma) in **HCV**
- **Non-liver-related mortality:**
  - **18** (6 Non-liver-related cancers, 3 cardiovascular, 1 HIV, 8 others) in **HIV/HCV**
  - **28** (3 Non-liver-related cancers, 4 cardiovascular, 21 others) in **HCV**

Table 2. Association between HIV co-infection and risk of liver-related events, liver-related mortality and non-liver-related mortality in HCV infected participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts

	Liver-related events		Liver-related mortality		Non-liver-related-mortality	
	HR* [CI95%]**	**p-value**	**HR* [CI95%**]**	**p-value**	**HR* [CI95%**]**	**p-value**
HCV¥	ref	0.30	ref	0.95	ref	0.01
HIV§/HCV¥	0.7 [0.3 ; 1.4]		1.0 [0.3 ; 3.2]		2.8 [1.3 ; 6.4]	

* Hazard Ratio, ** Confidence interval at 95%, ¥ Hepatitis C virus, § Human immunodeficiency virus

- After adjusting on confounding factors, in **HCV participants treated by DAA**, **HIV co-infection** was:
  - **Not associated** with the risk of **liver-related events** (HR: 0.7 [0.3 ; 1.4]) **neither** with the risk of **liver-related mortality** (HR: 1.0 [0.3 ; 3,.2])
  - **Associated** with a significant **increased risk** of **non-liver-related mortality** (HR: 2.8 [1.3 ; 6.4])

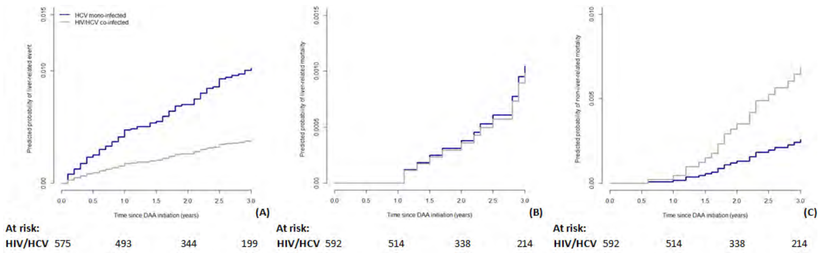


Figure 1. Predicted probabilities of liver-related events (A), liver-related mortality (B) and non-liver-related mortality (C) according to HIV co-infection in HCV infected participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts, estimated for mean participants

CONCLUSION

- **After DAA** treatment initiation **HIV co-infection** was **not associated** with the risk of **liver-related events** or **liver-related mortality**.
- **HIV co-infection** was **associated** with an **almost 3 times increase** of the **risk** of **non-liver-related mortality**.
- The **higher risk** of **non-liver-related mortality** could be explained by **chronic inflammation** and **immunosuppression** due to **HIV co-infection** but also to **higher risk behaviors** (like tobacco and alcohol consumption) in **HIV co-infected.**

Acknowledgements:
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, D. Lebrasseur-Longuet.

Clinical Centres (ward / participating physicians): APHP, Hôpitaux Universitaires Paris Centre, Paris (Médecine Interne et Maladies Infectieuses : D. Salmon, R. Usubillaga; Hépato-gastro-entérologie : P. Sogni ; Anatomo-pathologie : B. Terris ; Virologie :P. Tremeaux) ; APHP Pitié-Salpétrière, Paris (Maladies Infectieuses et Tropicales : C. Katlama, M.A. Valantin, H. Stitou ; Médecine Interne : A. Simon, P. Cacoub, S. Nafissa ; Hépato-gastro-entérologie : Y. Benhamou ; Anatomo-pathologie : 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; Anatomo-pathologie : P. Callard, F. Bendjaballah ; Virologie : C. Amiel, C. Le Pendeven) ; CHU Purpan, Toulouse (Maladies Infectieuses et Tropicales : B. Marchou ; Médecine interne : L. Alric ; Hépato-gastro-entérologie : K. Barange, S. Metivier ; Anatomo-pathologie : J. Selves ; Virologie : F. Larrouquette) ; CHU Archet, Nice (Médecine Interne : E. Rosenthal ; Infectiologie : A. Naqvi, V. Rio ; Anatomo-pathologie : J. Haudebourg, M.C. Saint-Paul ; Virologie : A. De Monte, V. Giordanengo, C. Partouche) ; APHP Avicenne, Bobigny (Médecine Interne – Unité VIH : O. Bouchaud ; Anatomo-pathologie : A. Martin, M. Ziol ; Virologie : Y. Baazia, V. Iwaka-Bande, A. Gerber) ; Hôpital Joseph Ducuing, Toulouse (Médecine Interne : M. Uzan, A. Bicart-See, D. Garipuy, M.J. Ferro-Collados ; Anatomo-pathologie : J. Selves ; Virologie : F. Nicot) ; APHP Bichat – Claude-Bernard, Paris (Maladies Infectieuses : A. Gervais, Y. Yazdanpanah; Anatomo-pathologie : H. Adle-Biassette ; Virologie : G. Alexandre, Pharmacologie : G. Peytavin) ; APHP Saint-Louis, Paris (Maladies infectieuses : C. Lascoux-Combe, J.M. Molina; Anatomo-pathologie : P. Bertheau; Virologie :M.L. Chaix, C. Delaugerre, S. Maylin) ; APHP Saint-Antoine (Maladies Infectieuses et Tropicales : K. Lacombe,; J. Krause, P.M. Girard, Anatomo-pathologie : D. Wendum, P. Cervera, J. Adam ; Virologie : C. Vialà) ; APHP, Hôpitaux Paris Sud, Bicêtre, Paris (Maladies Infectieuses et Tropicales : D. Vittecoq ; Médecine Interne : L. Goujard, Y. Quertainmont, E. Teicher; Virologie : C. Pallier) ; APHP Necker, Paris (Maladies Infectieuses et Tropicales : O. Lortholary, C. Duvivier, C. Rouzaud, J. Lourenco, F. Touam, C. Louisin ; Virologie : V. Avettand-Fenoel, E. Gardiennet, A. Mélard) ; CHU Bordeaux Hôpital Pellegrin, Bordeaux (Maladies Infectieuses et Tropicales : D. Neau, A. Ochoa, E. Blanchard, S. Castet-Lafarie, C. Cazanave, D. Malvy, M. Dupon, H. Dutronc, F. Dauchy, L. Lacaze-Buzy, A. Desclaux; Anatomo-pathologie : P. Bioulac-Sage ; Virologie : P. Trimoulet, S. Reigadas) ; CHU Bordeaux Hôpital Saint-André, Bordeaux (Médecine Interne et Maladies Infectieuses : Médecine Interne et Maladies Infectieuses : P. Morlat, D. Lacoste, F. Bonnet, N. Bernard, M. Hessamfar, J. F. Paccalin, C. Martell, M. C. Pertusa, M. Vandenhende, P. Mercié, D. Malvy, T. Pistone, M.C. Receveur, M. Méchain, P. Duffau, C Rivoisy, I. Faure, S. Caldato ; Anatomo-pathologie : P. Bioulac-Sage ; Virologie : P. Trimoulet, S. Reigadas, P. Bellecave, C. Tumiotto) ; CHU Bordeaux Hôpital du Haut-Levêque, Bordeaux (Médecine Interne : J.L. Pellegrin, J.F. Viallard, E. Lazzaro, C. Greib ; Anatomo-pathologie : P. Bioulac-Sage ; Virologie : P. Trimoulet, S. Reigadas) ; Hôpital FOCH, Suresnes (Médecine Interne : D. Zucman, C. Majerholc ; Virologie : M. Brollo, E. Farfour) ; APHP Antoine Béclère, Clamart (Médecine Interne : F. Boué, J. Polo Devoto, I. Kansau, V. Chambrin, C. Pignon, L. Bernoukrche, R. Fior, V. Martinez, S. Abgrall, M. Favier ; Virologie : C. Delback) ; CHU Henri Mondor, Créteil (Immunologie Clinique : Y. Lévy, S. Dominguez, J.D. Lelièvre, A.S. Lascaux, G. Melica) ; CHU Nantes Hôpital Hôtel Dieu, Nantes (Maladies Infectieuses et Tropicales : E. Billaud, F. Raffi, C. Allavena , V. Reliquet, D. Boutoille, C. Biron; M. Lefebvre, N. Hall, S. Bouchez ; Virologie : A. Rodallec, L. Le Guen, C. Hemon) ; Hôpital de la Croix Rousse, Lyon (Maladies Infectieuses et Tropicales : P. Miailhes, D. Peyramond, C. Chidiac, F. Ader, F. Biron, A. Boibieux, L. Cotte, T. Ferry, T. Perpoint, J. Koffi, F. Zoulim, F. Bailly, P. Lack, M. Maynard, S. Radenne, C. Augustin-Normand ; Virologie : C. Scholtes, T.T. Le-Thi) ; CHU Dijon, Dijon (Département d'Infectiologie ; L. Piroth, P. Chavanet M. Duong Van Huyen, M. Buisson, A. Waldner-Combernoux, S. Mahy, R. Binois, A.L. Simonet-Lann, D. Croisier-Bertin, A. Salmon Rousseau, C. Martins) ; CH Perpignan, Perpignan (Maladies infectieuses et tropicales : H. Aumaître, Virologie : S. Galim) ; CHU Robert Debré, Reims (Médecine interne, maladies infectieuses et immunologie clinique : F. Bani-Sadr, D. Lambert, Y Nguyen, J.L. Berger, M. Hentzien, Virologie : V. Brodard) ; CHRU Strasbourg (Le Trait d'Union : D Rey, M Partisani, Ms Batard, C Cheneau, M Priester, C Bernard-Henry, E de Mautort, Virologie : P Gantner et S Fafi-Kremer)

Data collection: F. Roustant, P. Platterier, I. Kmiec, L. Traore, M-K. Youssouf, A. Benmammar, M-G. Tateo, S. Lepuil, Pomes Chloé V. Sicart-Payssan, , S. Anrlamiandrosoa, C. Pomes, F. Touam, C. Louisin, M. Mole,P Catalan, M. Mebarki, A. Adda-Lievin, P. Thilbaut, Y. Ousidhoum, F.Z. Makhoukhi, O. Brak, R. Bayoud, C. Gatey, M.P. Pietri, V. Le Baut, R. Ben Rayana, F. Barret, C. Chesnel, D. Benken, M. Pauchard, S. Akel, S. Caldato, T. Rojas-Rojas, C. Debreux, L. Chalal, J.Zelie, A. Soria, M. Cavelliez, S. Breau, P. Fisher, C. Charles, D. Croisier-Bertin, S. Ogoudjobi, C. Brochier, V. Thoirain-Galvan, M. Le Cam.

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

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

Contact mail: mathieu.chalouni@u-bordeaux.fr