Excess mortality in HCV-treated PLWH with direct-acting antivirals compared to HIV monoinfection despite controlled HIV: Results from the ANRS-CO4 FHDH cohort

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Background

- Liver disease: one of the main causes of death in PLWH[1]
  - Partly attributable to HIV/HCV coinfection.
- Since 2014, DAAs for HCV: 95 % cure and ↓ hepatic complications[2,3].

Cure → sustained virologic response (SVR12)

= negative PCR 12 weeks after treatment completion.

Despite cure in HCV monoinfection:

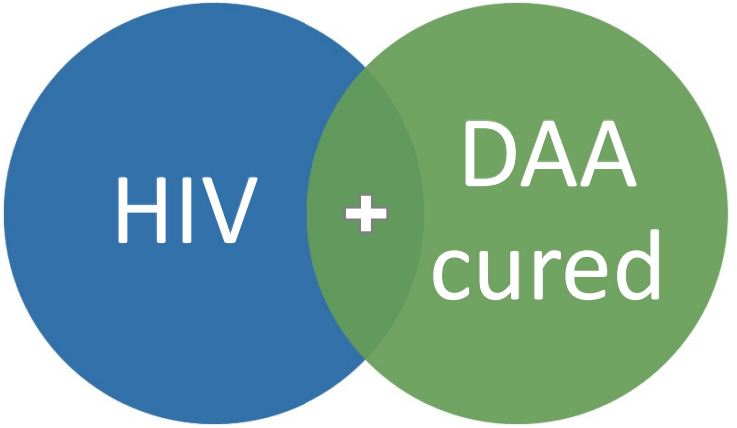
- Morbid events
  - alcohol and diabetes
- Excess mortality[4]
- Small number of studies on HIV/HCV coinfection[5]

Higher risk of death in DAA cured and HIV controlled patients ?

[1] Croxford S *et al.* 2017; [2] Carrat *et al.* 2019; [3] Janjua *et al.* 2021; [4] Butt *et al.* 2020; [5] Chalouni M *et al.* 2021

Objectives

I	II
• To identify **risk factors** associated with all-cause mortality in DAA cured PLWH achieving HIV viral suppression (<200 copies/mL)	• To compare **all-cause mortality** in people living with HIV (**PLWH**) achieving viral suppression (<200 copies/mL) **cured of HCV** by direct-acting antivirals (**DAA**) • To all-cause mortality in **HIV mono-infected** individuals under virological control • Adjusting for risk factors identified in (I)



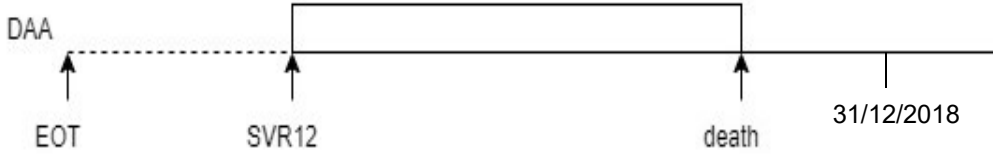
Objective I

Identification of risk factors associated with all-cause mortality in DAA cured PLWH

I. Methodology

Patients and methods:

- Inclusion : DAA sept 2013-sept 2018, adults.
- Exclusion : Boceprevir, Telaprevir.



Outcome:
All-cause mortality

ANRS-CO4 **FHDH**
204,529 PLWHIV-1
(1992-2018)

↓

13,844 HCV-RNA+

↓

3 599 PLWHIV-1 DAA cured
VL<200 c/mL w/6 mo SVR12
and CD4 available

Multivariable Cox proportional hazards model to estimate risk factors associated with mortality

adjusted for age, gender, HIV transmission route, AIDS status before SVR12, cirrhosis before HCV treatment, CD4 nadir, and BMI.

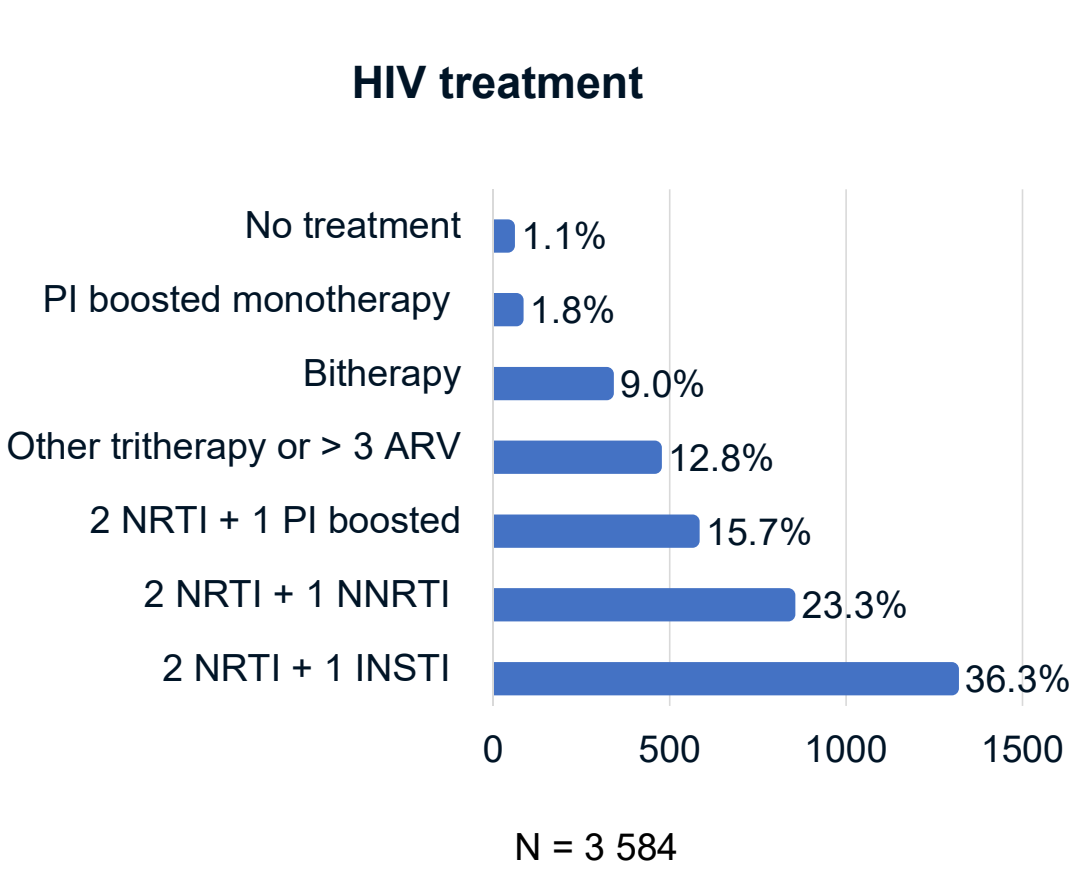
I. Results

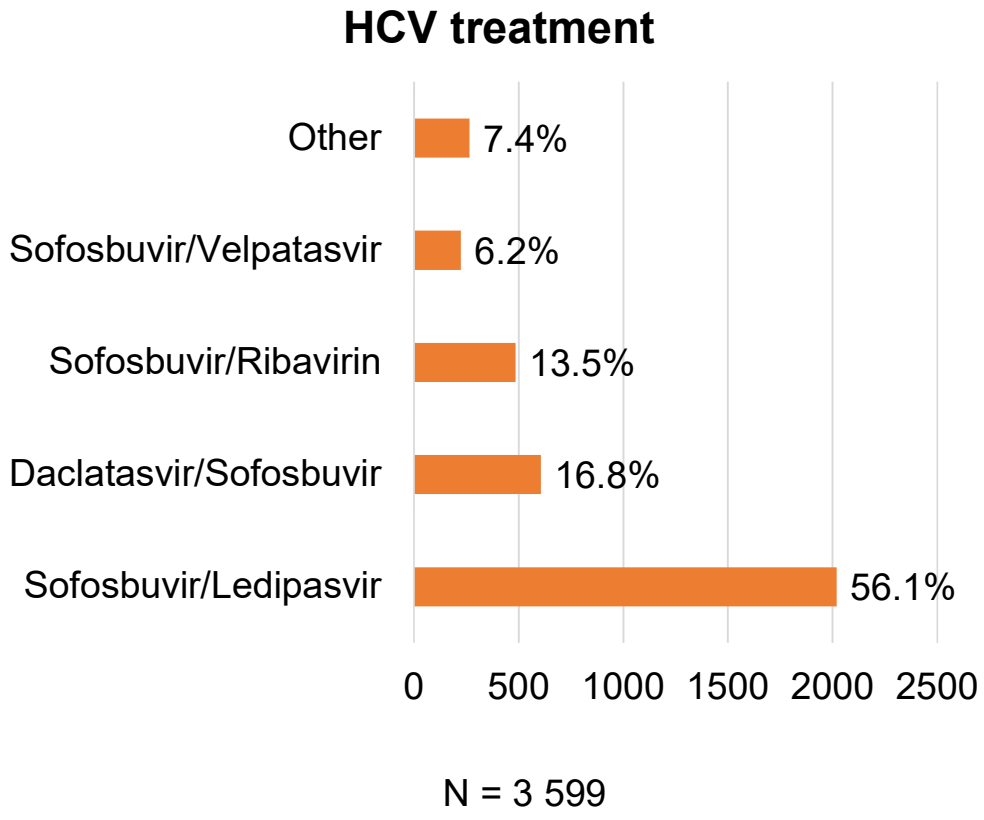
DAA cured, HIV VL < 200 copies/mL for 6 months before SVR12 (n =3 599)		
Characteristics at SVR12	**N**	**Median [IQR] or n (%)**
Age (years)	3,599	52.7 [48.4 ; 56.3]
Men	3,599	2 642 (73.4%)
Origin	3,599	
Metropolitan France		2 729 (75.8%)
Subsaharan Africa		252 (7.0%)
Other		618 (17.2%)
BMI (kg/m^2)	3,487	22.8 (20.4-25.3)
Time since first + HCV PCR (years)	3,564	7.4 [3.0 ; 11.2]
Transmission route HCV	3,599	
Intravenous drug user (IDU)		2 064 (57.3%)
Sexual		763 (21.2%)
Transfusion		117 (3.3%)
Unknown		485 (13.5%)
Other		170 (4.7%)
Cirrhosis before HCV treatment	3,599	316 (8.8 %)

I. Results

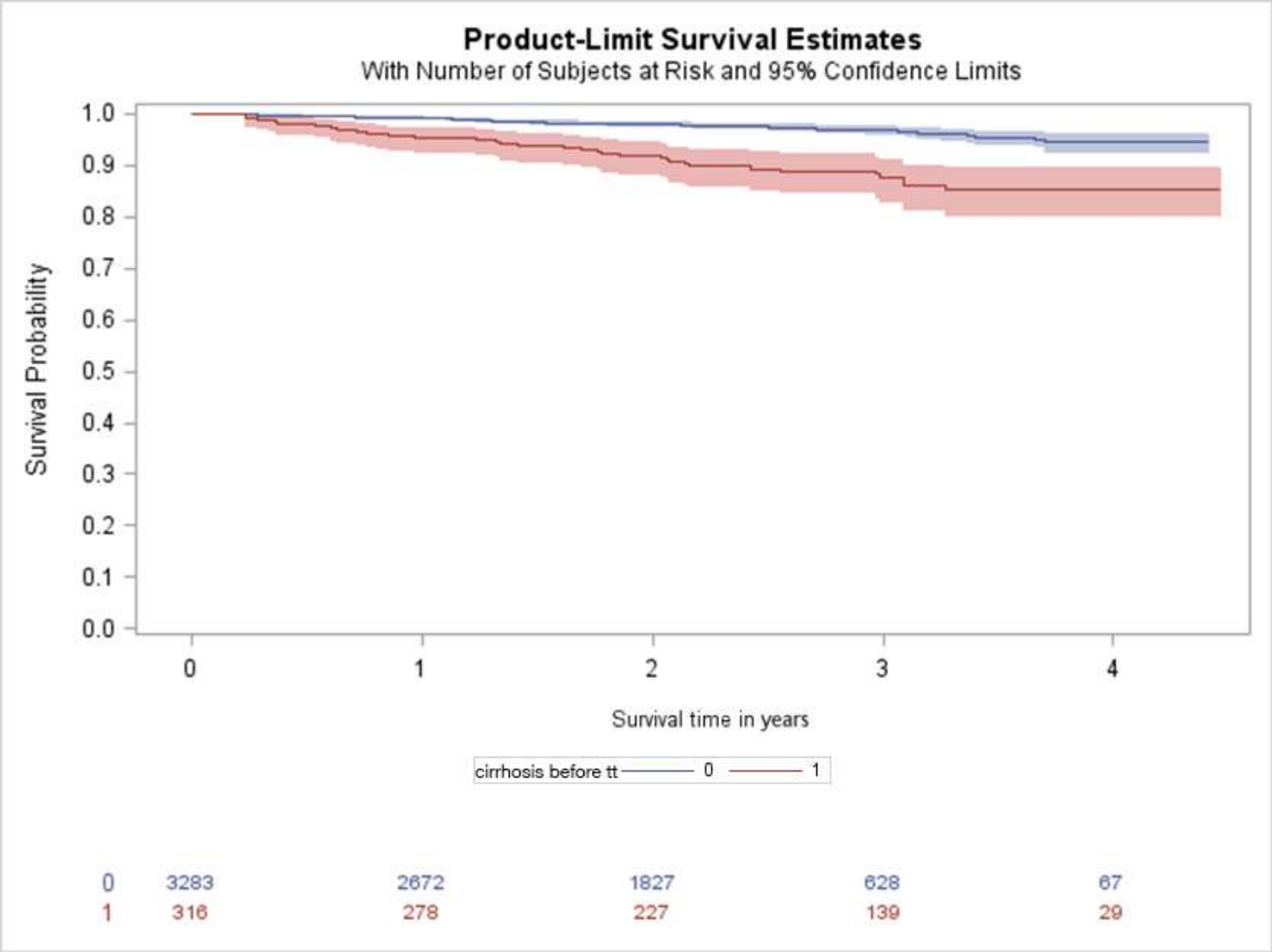
DAA cured, HIV VL <200 copies/mL (n =3 599)		
Characteristics at SVR12	**N**	**Median [IQR] or n (%)**
Smoking (first visit)	2,211	1078 (48.8%)
Alcohol (daily)	1,740	728 (22.0%)
None		1,040 (59.8%)
<40 g		577 (33.2%)
>40 g		123 (7.1%)
Treatment duration (weeks)	3,537	12.4 [12.0 ; 13.3]
Year of HCV treatment initiation	3,599	2015 [2015 ; 2016]
Year of first + HIV diagnosis	3,592	1992 [1987 ; 2002]
CD4 ± 6 months (c/mm^3)	3,599	658 [464 ; 886]
Nadir CD4 ± 6 months (c/mm^3)	3,599	169 [75 ; 285]
AIDS	3,599	925 (25.7%)

I. Results


HIV treatment
No treatment
1.1%
PI boosted monotherapy
1.8%
Bitherapy
9.0%
Other tritherapy or > 3 ARV
12.8%
2 NRTI + 1 PI boosted
15.7%
2 NRTI + 1 NNRTI
23.3%
2 NRTI + 1 INSTI
36.3%
0
500
1000
1500
N = 3 584


HCV treatment
Other
7.4%
Sofosbuvir/Velpatasvir
6.2%
Sofosbuvir/Ribavirin
13.5%
Daclatasvir/Sofosbuvir
16.8%
Sofosbuvir/Ledipasvir
56.1%
0
500
1000
1500
2000
2500
N = 3 599

I. Results

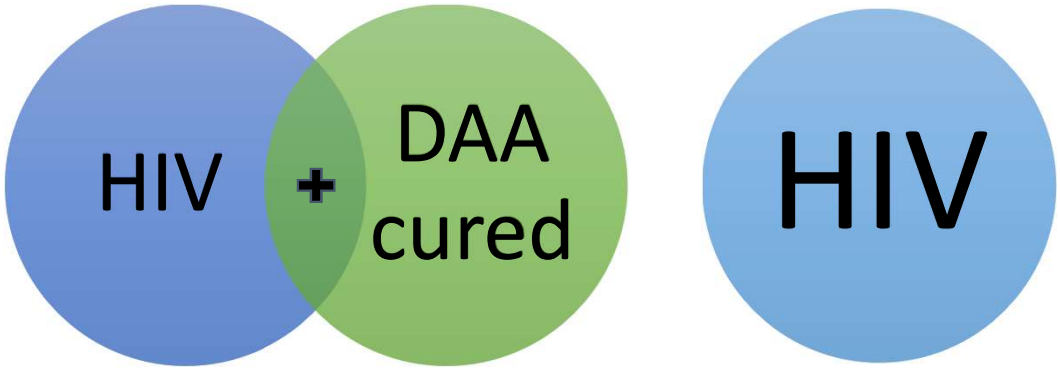

Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Confidence Limits
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
Survival time in years
cirrhosis before tt
0
1
0 3283 2672 1827 628 67
1 316 278 227 139 29

I. Results

Risk factors associated with mortality in DAA cured HIV/HCV coinfected participants

Multivariable analysis (Cox)	N	deaths	HR	*p*
Transmission route HIV				*0.05*
MSM	873	11	1.00	
IDU	1 605	73	1.89 [0.97-3.69]	
Other	1 121	27	1.22 [0.58-2.57]	
Men	2 649	80	1.06 [0.68-1.66]	*0.79*
Age at SVR12 (years)				***0.02***
<50	1 185	17	1.00	
50-60	2 022	77	1.79 [1.04-3.06]	
≥ 60	392	17	2.54 [1.29-5.01]	
AIDS before SVR12	925	39	1.18 [0.78-1.79]	*0.43*
CD4 Nadir (log2 c/mL)	3 599	111	0.98 [0.89-1.09]	*0.70*
Cirrhosis before SVR12	316	35	3.56 [2.36-5.37]	*<0.001*
Alcohol	702	30	1.82 [1.10-2.99]	*0.02*
BMI (kg/m^2)				***0.01***
<18.5	446	21	2.14 [1.30-3.55]	
18.5-24.99	2 223	65	1.00	
≥ 25	930	25	0.92 [0.58-1.47]	

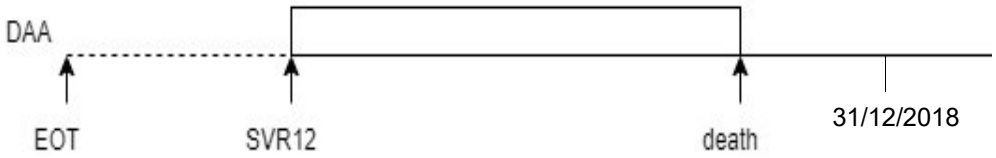
Objective II



Mortality comparison between DAA cured HIV/HCV coinfected and HIV monoinfected

II. Methodology

Patients and methods:



French Hospital Database on Hiv

3 599 PLWHIV-1 DAA cured VL<200 c/mL w/6 mo SVR12 and CD4 available

ANRS-CO4 FHDH **cured HCV** participants

>18 years old controlled HIV viral load (VL)

started DAAs between 09- 2013 and 09-2018.

Matched on

- age (+/- 5 years)
- gender
- HIV transmission route (men who have sex with men -MSM- intravenous drug user -IVDU- or other)
- AIDS status
- BMI (+/- 1)

To up to 10 **HIV mono-infected** patients

with controlled HIV VL followed at the index date (date of SVR12).

Poisson regression with robust variance estimates

adjusted for age, gender, HIV transmission route, AIDS status, year of first HIV diagnosis, CD4 nadir, and BMI.

Outcome:
All-cause mortality

Analyses were performed at 0-36, 0-18 months and 18-36 months of follow-up.

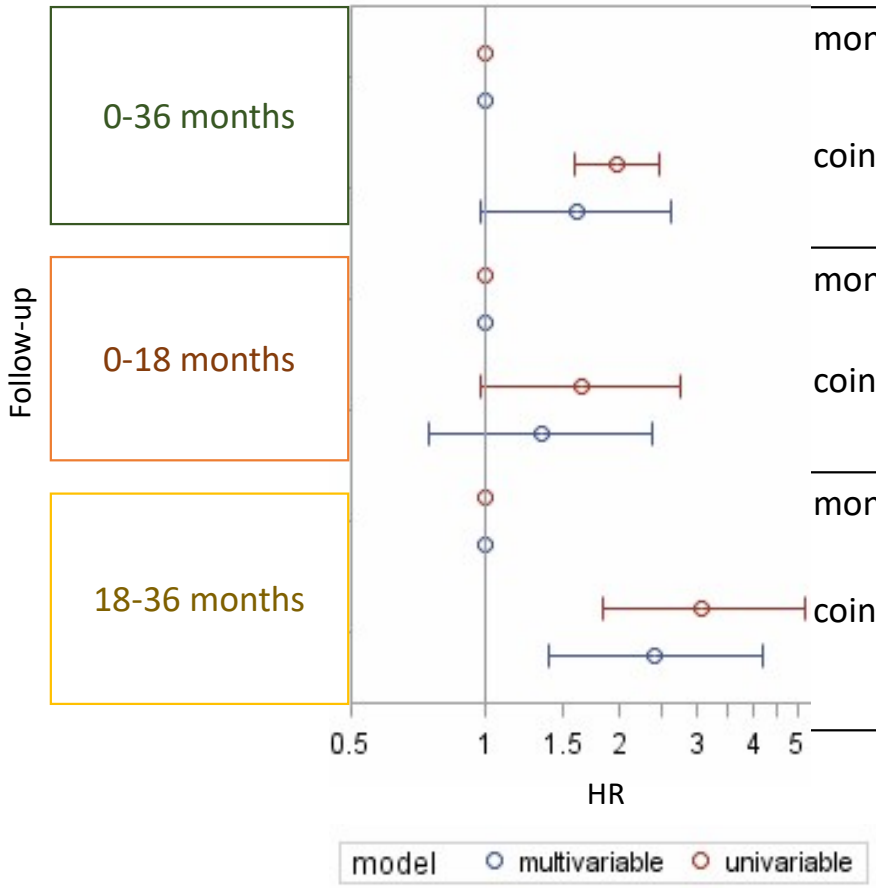
II. Results

	HIV VL < 200 copies/mL for 6 months before exposed SVR12 date			
	E-: HIV monoinfected. (n = 28,846)		E+: HIV/HCV coinfected cured by DAA. (n =3,574)	
Characteristics at SVR12 +/- 6 mo	**N**	Median [IQR] or n (%)	**N**	Median [IQR] or n (%)
Age (years)	28 846	52.0 [47.2 ; 55.9]	3 574	52.6 [48.4 ; 56.3]
Men	28 846	22 085 (76.6%)	3 574	2 649 (74.1%)
Origin	28 846		3 574	
Metropolitan France		19 459 (67.5%)		2 706 (75.7%)
Sub-Saharan Africa		4 751 (16.5%)		252 (7.1%)
Other		4 636 (16.1%)		616 (17.2%)
HIV transmission route	28 846		3 574	
IDU		9 135 (31.6%)		1 580 (44.2%)
MSM		8 686 (30.1%)		873 (24.4%)
Other		11 025 (38.2%)		1121 (31.4%)

II. Results

	HIV VL < 200 copies/mL for 6 months before exposed SVR12 date			
	E-: HIV monoinfected. (n = 28,846)		E+: HIV/HCV coinfected cured by DAA. (n =3,574)	
Characteristics at SVR12 +/- 6 months	**N**	Median [IQR] or n (%)	**N**	Median [IQR] or n (%)
Year of first HIV+ diagnosis	28,789	1999 [1992 ; 2008]	3,567	1992 [1987 ; 2002]
Time having VL <200 copies/mL (years)	28,846	7.87 [3.36 ; 12.25]	3,574	9.31 [5.46 ; 13.62]
AIDS before index date	28,846	5,988 (20.8%)	3,574	900 (25.2%)
BMI (kg/m2)	28,844	23.1 [21.0; 25.4]	3,426	22.8 [20.4 ; 25.3]
CD4 ± 6 months (cells/mm3)	28,846	633 [442 ; 860]	3,574	631 [442 ; 867]
CD4 Nadir ± 6 months (cells/mm3)	28,846	211 [86 ; 340]	3,574	170 [76 ; 286]
Alcohol (daily)	4,165		1,740	
None		2,680 (64.4%)		1,040 (59.8%)
<40 g		1,270 (30.5%)		577 (33.2%)
>40 g		215 (5.2%)		123 (7.1%)

II. Results



Exposure	N	IRR 95% CI	Person-years	deaths	Incidence / 1000 PY
monoinfected	28,846		53,435	376	7.0 [6.4;7.8]
coinfected	3,754	1.97 [1.25;3.10] **1.59 [0.97;2.62]***	7,135	99	13.9 [11.3;16.8]
monoinfected	28,846		35,779	292	8.2 [7.3 ; 9.1]
coinfected	3,754	1.65 [0.98;2.76] **1.34 [0.76;2.38]***	4,608	62	13.5 [10.4 ; 17.1]
monoinfected	18,837		17,656	84	4.8 [3. 8 ; 5.9]
coinfected	2,540	3.08 [1.83;5.13] **2.42 [1.40;4.20]***	2,526	37	14.7 [10.5 ; 20.0]

*adjusted for age, gender, HIV transmission route, AIDS status, year of first HIV diagnosis, CD4 nadir, and BMI.

II. Conclusion

- **Higher** risk of death in first 36 months of SVR in DAA cured HIV/HCV co-infected patients / HIV mono-infected patients (HR = 1.60)
  - ➢ **despite** HCV cure, HIV viral suppression and after controlling for variables associated with mortality.

- **Similar** absolute risk of death in HIV/HCV coinfected participants cured by DAAs between **0-18 months** and **18-36 months**
  - ➢ while **lower** risk of death in HIV monoinfected participants in the 18-36 months / 0–17 months period.

Previous findings :

Higher all-cause mortality in coinfected	**Mortality drop in HIV patients**
Alejos B. *et al* Medicine 2016 May MT. *et al* J Acquir Immune Defic Syndr. 2015 Chalouni M. *et al* J Hepatol 2020	Fontela C *et al*. Sci Rep 2020 Croxford *et al.* Lancet Public Health. 2017

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TEAM

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