

# Higher all-cause mortality in individuals living with HIV cured of HCV by direct-acting antivirals compared to HIV mono-infection despite controlled HIV: Results from the ANRS-CO4 FHDH cohort

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## INTRODUCTION

Liver disease is one of the leading causes of mortality among people who live with HIV (PLWH), in part due to hepatitis coinfection (1).

Since 2014, direct-antiviral agents (DAAs) have enabled a 95% cure rate (measured by SVR12) and decreased hepatic complications in mono-infected patients with Hepatitis C virus (HCV) (2).

Despite HCV cure, there is an increased risk of death and morbid events in mono-infected individuals (3,4).

Few studies exist in HIV/HCV coinfecting patients (5).

## AIM

To compare all-cause mortality in PLWH achieving HIV viral suppression (< 200 copies/mL) cured of HCV by DAAs to all-cause mortality in virally suppressed HIV mono-infected individuals of the nationwide ANRS-CO4 French Hospital Database on HIV (FHDH) cohort.

## METHOD

### Population:

Exposed (E+): HIV/HCV coinfecting cured by DAA



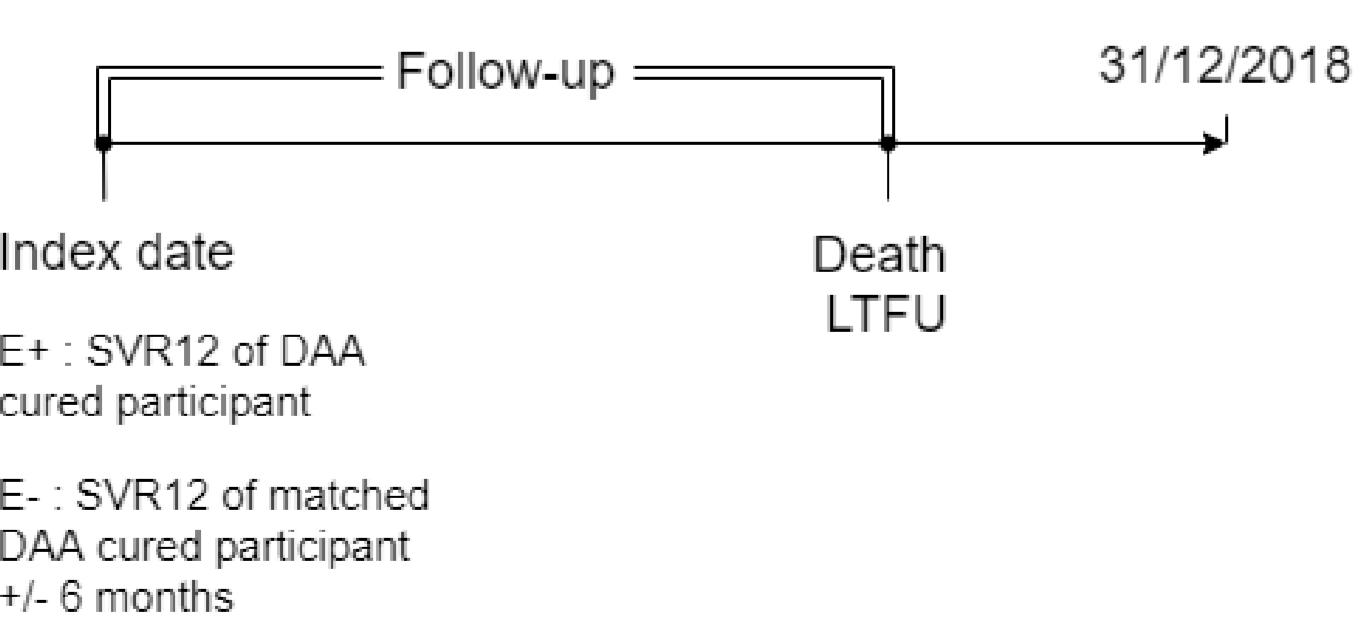
Unexposed (E-): HIV mono-infected

ANRS-CO4 FHDH cured HCV participants >18 years old with controlled HIV viral load who started DAAs between September 2013 and September 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, and BMI (+/- 1)

To up to 10 HIV mono-infected patients with controlled HIV viral load (VL), followed at the index date (date of SVR12).

### Follow-up period:



**Outcome:** All-cause mortality.

**Statistical analysis:** Multivariable Cox proportional hazards models with robust variance estimates were used to compare mortality in both groups adjusting for age, gender, HIV transmission route, AIDS status, year of first HIV serology, CD4 nadir, and BMI.

Analysis were performed at 0-36, 0-17 months and 18-36 months of follow-up.

## RESULTS

Sample: **3 574 HCV** infected participants cured by DAAs, co-infected by HIV and with at least one VL < 200 copies/mL within 6 months before SVR12;

matched to 28 846 HIV mono-infected participants, followed at the index date and after, with at least one VL < 200 copies/mL 6 months before the index date.

Table 1. Baseline participant characteristics according to HCV cure

Characteristics at index date (exposed SVR12 +/- 6 months)	E-: HIV mono-infected. HIV VL < 200 copies/mL for 6 months before exposed SVR12 date (n = 28,846)		E+: HIV/HCV coinfecting cured by DAA. HIV VL < 200 copies/mL for 6 months before SVR12 (n = 3,574)	
	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%)		1,121 (31.4%)
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/m <sup>2</sup> )	28,844	23.1 [21.0 ; 25.4]	3,426	22.8 [20.4 ; 25.3]
CD4 ± 6 months (cells/mm <sup>3</sup> )	28,846	633 [442 ; 860]	3,574	631 [442 ; 867]
CD4 Nadir ± 6 months (cells/mm <sup>3</sup> )	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%)

Figure 1. Probability of death according to HIV/HCV coinfection – data censored at 36 months

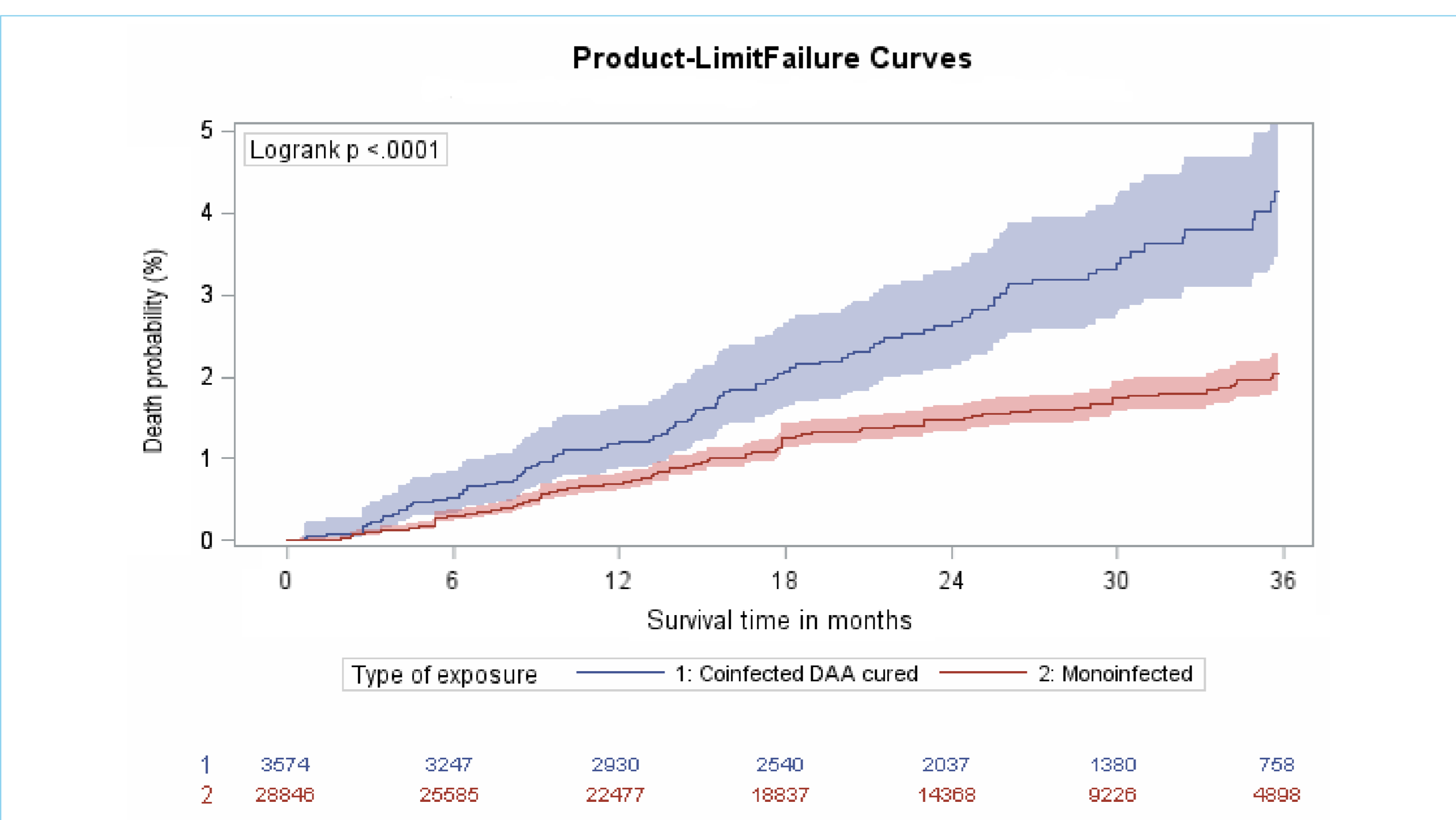


Table 2. Adjusted analysis for the association of HIV/HCV coinfection group and mortality - data censored at 36 months

Multivariable analysis (Cox)	N	deaths	3-year survival [95% CI]	HR	p
Exposure group					0.06
E-: HIV mono-infected	28,846	376	0.980 [0.977;0.982]	1.00	
E+: HIV/HCV coinfecting DAA cured	3,574	99	0.957 [0.947;0.966]	1.60 [0.98;2.62]	
HIV transmission group					0.12
MSM	9,559	95	0.982 [0.977;0.986]	1.12 [0.59;2.15]	
IDU	10,715	256	0.967 [0.962;0.971]	1.75 [1.02;3.01]	
Other	12,146	124	0.984 [0.980;0.987]	1.00	
Gender					0.05
Female	7,686	76	0.981 [0.975;0.985]	1.00	
Male	24,734	399	0.976 [0.973;0.978]	1.63 [1.01;2.64]	
Age at SVR12 (years)					0.001
<50	12,223	113	0.983 [0.979;0.986]	1.00	
50-60	16,644	271	0.976 [0.973;0.979]	1.14 [0.62;2.12]	
≥ 60	3,553	91	0.958 [0.946;0.966]	2.49 [1.37;4.54]	
First HIV diagnosis					0.24
< 2000	17,567	356	0.970 [0.967;0.973]	1.00	
≥ 2000	14,789	119	0.986 [0.983;0.989]	0.70 [0.39;1.27]	
AIDS before SVR12					0.89
no	25,532	350	0.979 [0.977;0.981]	1.00	
yes	6,888	125	0.970 [0.963;0.975]	0.96 [0.54;1.70]	
CD4 nadir (cells/mm <sup>3</sup> )					0.03
<200	15,750	336	0.969 [0.965;0.972]	1.00	
200-349	9,286	101	0.982 [0.978;0.986]	0.60 [0.28;1.29]	
≥ 350	7,384	38	0.990 [0.985;0.993]	0.34 [0.15;0.77]	
BMI (kg/m <sup>2</sup> )					0.11
<18.5	1,772	46	0.967 [0.956;0.975]	1.90 [0.86;4.23]	
≥ 18.5	30,498	428	0.978 [0.975;0.980]	1.00	

Table 3. Association between HIV/HCV coinfection group and mortality by follow-up time

Analysis	Overall censored at 36 months		0-18 months		18-36 months	
	N	deaths	N	deaths	N	deaths
Mono-infected	28 846	376	28 846	292	18 837	84
Coinfected	3 754	99	3 754	62	2 540	37
			value	95% CI	value	95% CI
Mono-infected Incidence / 1000 PY			7.0	[6.4 ; 7.8]	8.2	[7.3 ; 9.1]
Coinfected Incidence / 1000 PY			13.9	[11.3 ; 16.8]	13.5	[10.4 ; 17.1]
Incidence Rate Ratio E+/E-			1.97	[1.58 ; 2.46]	1.65	[1.25 ; 2.17]
HR E+/E- Cox Univariable			1.98	[1.58 ; 2.47]	1.64	[0.98 ; 2.75]
HR E+/E- Cox Multivariable*			1.60	[0.98 ; 2.62]	1.34	[0.75 ; 2.37]
			2.41	[1.39 ; 4.19]		

\*adjusted on age, gender, HIV transmission route, AIDS status, year of first HIV serology, CD4 nadir, and BMI

## CONCLUSIONS

- The risk of death in the first 36 months of SVR is higher in DAA cured HIV/HCV co-infected patients than in HIV mono-infected patients, despite HCV cure, HIV viral suppression and after controlling for CD4 nadir, age, gender, HIV transmission route, AIDS status, year of first HIV diagnosis and BMI.
- The absolute risk of death in HIV/HCV coinfecting participants cured by DAAs remains constant between 0-18 months and 18-36 months, while the risk of death in HIV mono-infected participants is much lower in the 18-36 months period compared to the 0-18-month period.
- An update of the database will allow us to see if these results are confirmed with a longer follow-up.

## ACKNOWLEDGEMENTS

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→ For more information visit <https://anrs-co4.fhdh.fr/>

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