0915 - MORTALITY RATES AND CAUSES OF DEATH ACCORDING TO INCLUSION PERIOD IN HIV/HCV PATIENTS

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CONTEXT

- HIV/HCV co-infected patients have an higher risk of mortality in comparison to HCV mono-infected patients.
- Due to efficient and well-tolerated direct acting antivirals (DAA), liver disease progression has slowed down both in HCV mono-infected and HIV/HCV co-infected patients (1).
- Therefore, changes in incidences and in mortality causes may occur since large access to DAA.

Objectives:

- To study mortality and the underlying causes of death at 3 years according to 3 inclusion periods (reflecting treatment periods) in the french nationwide ANRS CO13 HEPAVIH cohort of HIV/HCV co-infected patients.

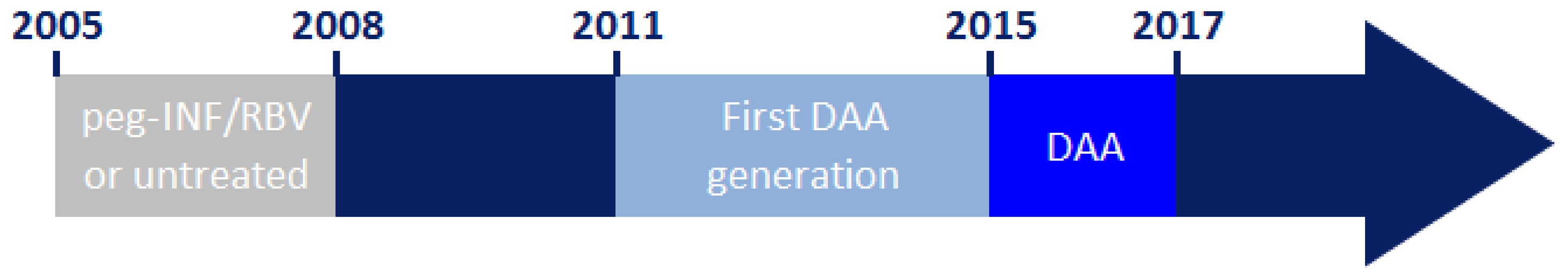
METHODS

Population: All participants chronically infected by HCV and HIV included in the ANRS CO13 HEPAVIH.

Baseline: Date of inclusion in the ANRS CO13 HEPAVIH cohort.

Definition of inclusion periods:

- Before 2011, reflecting absence of therapy or treatment by pegylated-interferon and ribavirin.
- Between 2011 and 2014, reflecting treatment with first generation DAA.
- After 2014, reflecting treatment with second generation DAA.



Follow-up: Participant's follow-up ended at time of occurrence of death, last follow-up visit or three years after baseline, whichever came first.

Main outcome: All-cause mortality (Causes of death were reviewed and classified by a validation committee).

Secondary outcome:

- Cause specific mortality: Liver-related, HIV, non-HCV non-HIV cancer-related, cardiovascular, other causes (unknown, suicide, overdose, hemorrhage, septic shock, etc.)

Statistical analysis:

- Estimation of all-cause mortality rates and cause specific mortality rates using Aalen-Johansen method accounting for competitive risks.
- Estimation of the impact of inclusion period on the risk of all-cause and cause specific mortality evaluated using Cox proportional or cause-specific Cox proportional hazard models respectively, adjusted on age, sex, cirrhosis, baseline CD4 and baseline HIV viral load.

RESULTS

Population: 1710 chronically HCV infected patients co-infected by HIV (database May 2018).

- **1175** were included, during the pre-DAA era
- **212** between 2011 and 2014, during the first DAA generation-era
- **323** after 2014, during the DAA-era

Table 1. HCV-treatment outcomes by inclusion period in the cohort, in participants from the ANRS CO13 HEPAVIH *(n = 1710)*

Period	Untreated	Treated with unknown SVR* status	Treated without SVR*	Treated with SVR*
Before 2011	319 (27.2%)	62 (5.3%)	404 (34.4%)	390 (33.2%)
Between 2011 and 2014	3 (1.4%)	9 (4.3 %)	60 (28.3%)	140 (66.0%)
After 2014	8 (2.5%)	45 (13.9%)	75 (23.2%)	195 (60.4%)

*Sustained virological response, defined by an undetectable HCV viral load at least 12 or 24 weeks after the end of HCV treatment

Table 2. Characteristics at time of inclusion in the cohort by periods, for participants of the ANRS CO13 HEPAVIH *(n = 1710)*

	Before 2011 *(n = 1175)*	Between 2011 and 2014 *(n = 212)*	After 2014 *(n = 323)*
Characteristics	Median [IQR¥] or n (%)	Median [IQR¥] or n (%)	Median [IQR¥] or n (%)
Age *(years)*	44.9 [41.9 ; 48.2]	52.1 [48.8 ; 55.3]	52.2 [48.7 ; 56.4]
Men	826 (70.3%)	166 (78.3%)	250 (77.9%)
Current alcohol consumption	573 (49.3%)	81 (38.8%)	150 (48.4%)
Current tobacco consumption	832 (71.8%)	81 (38.8%)	168 (54.2%)
BMI^Δ *(kg/m²)*	21.6 [19.7 ; 24.1]	22.8 [21.0 ; 25.0]	22.4 [20.7 ; 25.2]
Time since first HCV‡ seropositivity *(years)*	10.0 [6.0 ; 14.0]	18.0 [12.0 ; 22.0]	16.0 [7.0 ; 22.0]
HCV‡ transmission group			
Intravenous drug users	642 (66.7%)	149 (71.0%)	177 (55.7%)
Homosexual	54 (5.6%)	19 (9.0%)	58 (18.2%)
Heterosexual	36 (3.7%)	7 (3.3%)	21 (6.6%)
Others	230 (23.9%)	35 (16.7%)	62 (19.5%)
History of anti-HCV‡ treatment	648 (55.1%)	47 (22.2%)	99 (30.7%)
Sustained virological response at baseline	120 (10.2%)	25 (11.8%)	36 (11.1%)
Cirrhotic*	204 (17.4%)	89 (42.2%)	66 (20.7%)
AIDS^Ψ CDC§ stage	328 (28.0%)	68 (32.5%)	91 (29.6%)
CD4 count (cells/mm³)	444.0 [305.0 ; 638.0]	550 [362.0 ; 734.0]	643.0 [419.0 ; 833.0]
Detectable HIV¤ viral load	362 (30.9%)	26 (12.3%)	33 (10.3%)
Ongoing ARV** therapy	1067 (92.8%)	208 (99.5%)	309 (99.4%)

¥ Interquartile range, Δ Body mass index, ‡Hepatitis C virus, * defined by a liver stiffness value superior to 12.5 kPa or a FIB-4 value superior to 3.25 for participants without liver stiffness measurement, ¤Human immunodeficiency virus, §Center for disease control and prevention, ** Antiretroviral, Ψ Acquired Immunodeficiency Syndrome

Table 3. Number of deaths 3 years after baseline by inclusion period, for participants of the ANRS CO13 HEPAVIH *(n = 1710)*

Period	Overall	Liver-related	HIV	Cardiovascular	Non-HCV non-HIV cancer	Others
Before 2011	63	28	8	3	9	15
Between 2011 and 2014	12	6	0	0	1	5
After 2014	9	1	0	2	2	4

- In crude analysis, liver-related mortality was the first cause of death before 2011 (25.4 per 1000 PY) and between 2011 and 2014 (39.1 per 1000 PY) but the third after 2014 (13.4 per 1000 PY).
- We observed a significant increase of the mortality from other causes (13.6, 31.9 and 98.3 per 1000 PY, p = 0.0331) and a trend for an increase of cardiovascular mortality (2.7 per 1000 PY before 2011 and 13.0 per 1000 PY after 2014, p = 0.0667)

Figure 1. Crude cumulative incidence of all-cause and cause specific death by inclusion period in the cohort, in participants from the ANRS CO13 HEPAVIH *(n = 1710)*

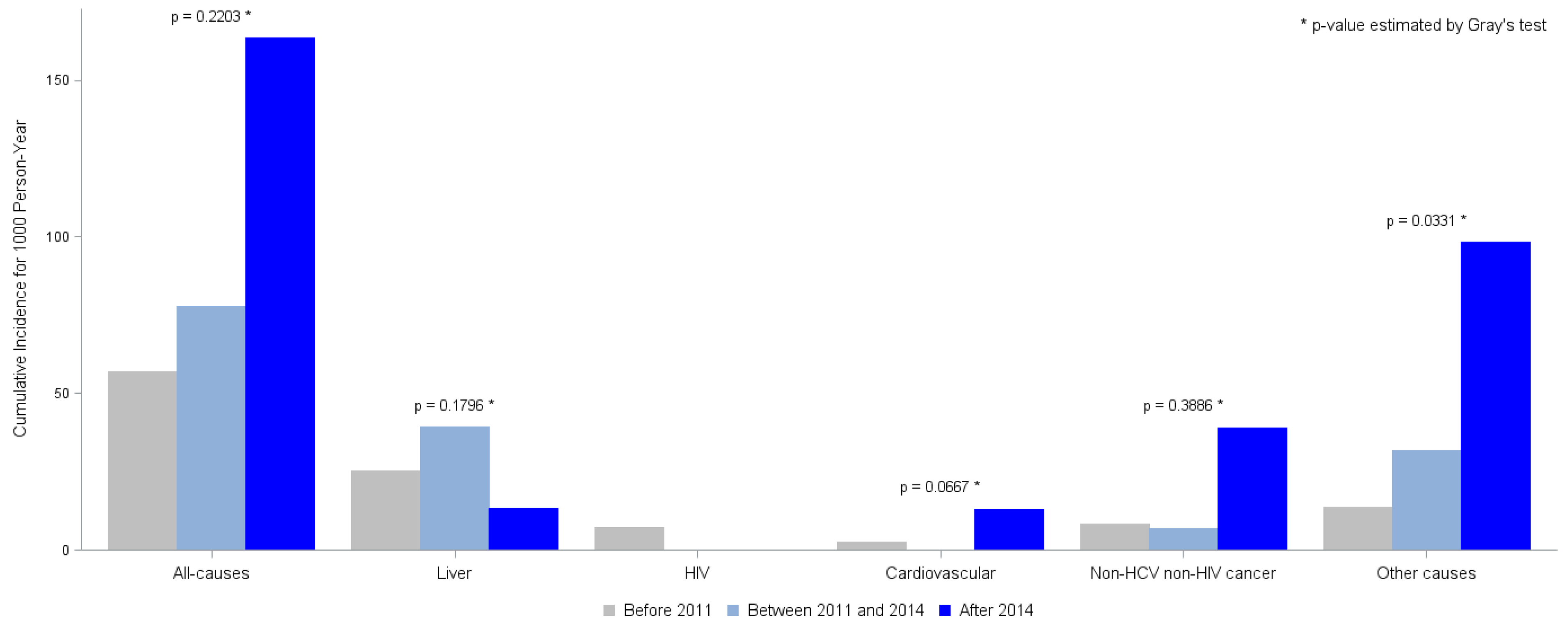


Figure 2. Incidence of cause specific mortality by inclusion period, for participants from the ANRS CO13 HEPAVIH cohort *(n = 1710)*

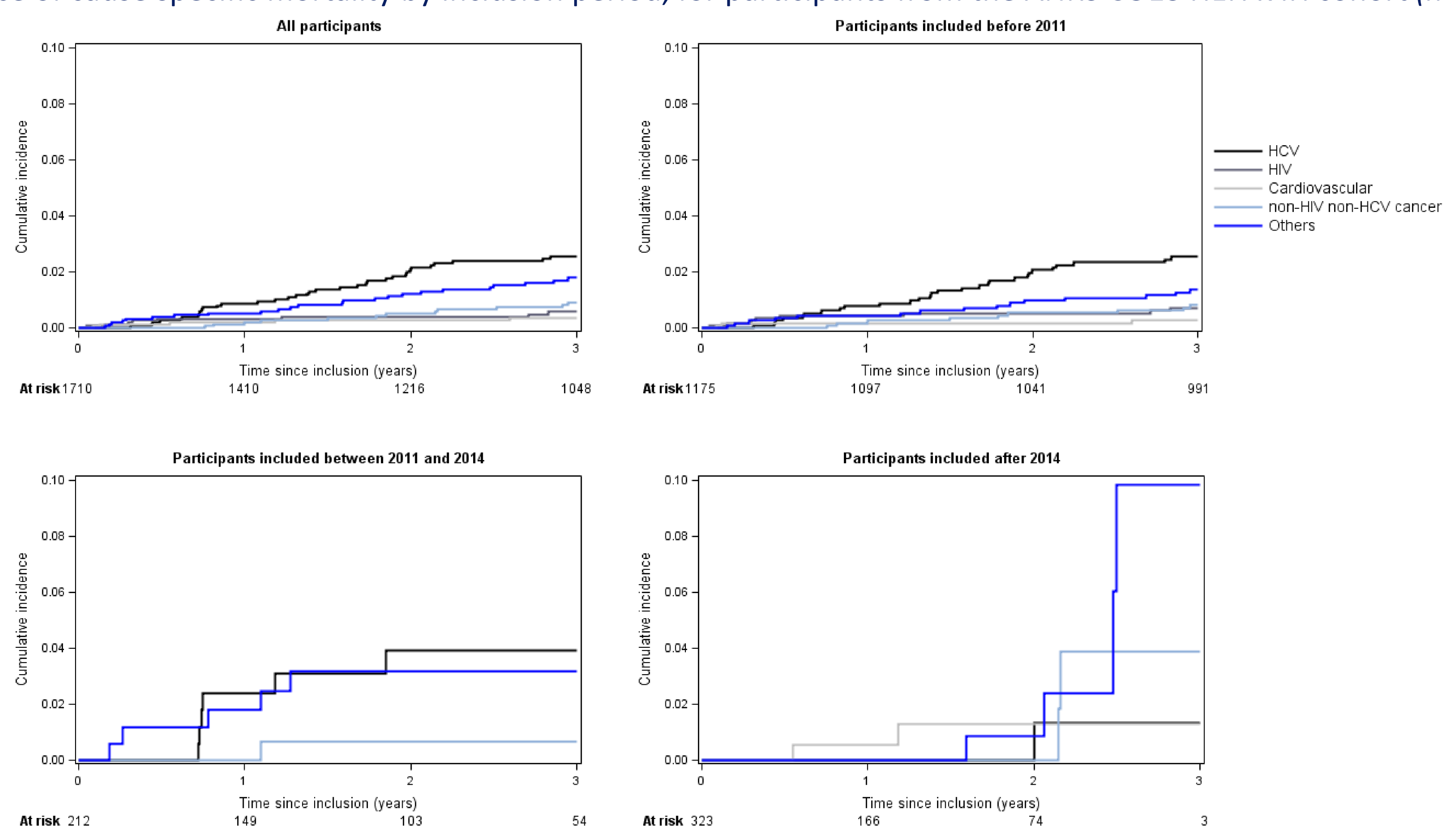


Table 2. Association between inclusion period and mortality, in adjusted analysis in participants from the ANRS CO13 HEPAVIH cohort *(n = 1710)*

	Overall*			Liver-related*			Cardiovascular*			Non-HCV non-HIV cancer*			Other*		
Period	HR	$CI_{95\%}$	p	HR	$CI_{95\%}$	p	HR	$CI_{95\%}$	p	HR	$CI_{95\%}$	p	HR	$CI_{95\%}$	p
Before 2011	ref	-	0.9946	ref	-	0.3916	ref	-	0.3250	ref	-	0.7361	ref	-	0.3127
2011 - 2014	1.0	[0.5 ; 2.0]		1.0	[0.4 ; 2.7]		-	-		0.5	[0.1 ; 4.6]		2.2	[0.7 ; 6.9]	
After 2014	1.0	[0.5 ; 2.2]		0.2	[0.0 ; 1.9]		5.5	[0.6 ; 51.4]		1.4	[0.2 ; 8.2]		2.2	[0.6 ; 7.7]	

* Adjusted on age, sex, cirrhosis (defined by a liver stiffness value superior to 12.5 kPa or a value of FIB-4 score superior to 3.25 for participants without liver stiffness measurement), CD4 count (in cells/mm³), detectable HIV viral load

- After adjusting on age, sex, cirrhosis, baseline CD4 count and baseline HIV viral load, the risk of all-cause mortality or any cause specific mortality was not different between the different inclusion periods.

CONCLUSION

- All-cause mortality at three-years of follow-up did not significantly change according to the three inclusion periods.
- Furthermore, after adjusting for important known risk factors, no specific trend for a significant change of underlying causes of death was identified.
- Nonetheless, it is important to note that no-HIV related death was observed three years after inclusion in patients included after 2011 and that the pattern if underlying causes of death seems to change between the three periods.

References

1. Salmon-Ceron D, Nahon P, Layese R, Bourcier V, Sogni P, Bani-Sadr F, et al. HIV/HCV co-infected cirrhotic patients are no longer at higher risk for HCC or end-stage liver disease as compared to HCV mono-infected patients. Hepatol Baltim Md. 2018 Dec 19.

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