



Regional Differences across Europe in Advanced Fibrosis and Cirrhosis among HIV/HCV Co-infected Persons between 2010-2015

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BACKGROUND

The increasing availability of directly acting antivirals (DAAs) for the treatment of hepatitis C coinfected persons has in some countries led to targeting DAAs to those most at need (fibrosis $\geq F3$) because of their cost. The prevalence of fibrosis $\geq F3$ across Europe is largely unknown, nor is the extent to which it is changing in different regions of Europe.

AIMS:

- To investigate regional differences in the prevalence of fibrosis $\geq F3$ or liver events in persons co-infected with HIV/HCV.
- To investigate factors associated with developing fibrosis $\geq F3$ and how this changes over time across different regions.

METHODS:

- Individuals co-infected with chronic HCV (defined as being HCV-AB positive and HCV-RNA positive) with a liver fibrosis biomarker (liver biopsy, APRI, hyaluronic acid or FibroScan) result whilst under follow-up in EuroSIDA on January 1st each year from 2010 to 2015 were included in this study.
- The proportion of HCV-RNA positive patients with fibrosis METAVIR $\geq F3$ or liver events (hepatic decompensation, hepatocellular carcinoma) was compared between regions over time. Fibrosis $\geq F3$ was defined by:

Liver fibrosis biomarker	Result
Liver biopsy	$\geq F3$
APRI	score ≥ 1.75
Hyaluronic acid	$>250\text{ng/mL}$
FibroScan	$\geq 9\text{kPa}$

- Adjusted odds ratio of an individual having fibrosis $\geq F3$ was assessed using logistic regression. Generalised estimating equations were used to allow the inclusion of individuals under follow-up in multiple years. This method was also used to investigate the effect of time within each region on the odds of developing fibrosis $\geq F3$.

RESULTS:

- There were 3712 individuals with chronic HCV and a liver fibrosis biomarker in the study, 965 of which had fibrosis $\geq F3$ at some point during follow-up (characteristics of patients shown in **Table 1**). 1411, 1367, 1317, 1382, 1371 and 2121 persons were under follow-up on 1/1/2010-2015 respectively.
- The proportion of individuals with fibrosis $\geq F3$ under follow-up on 1/1/2010-2015 was 20.3%, 22.9% 21.3% 20.4% and 23.0% respectively (**Figure 1**); with significant differences between regions each year ($p < 0.0001$).
- The greatest increase over time was in Northern and Southern Europe (17.0% to 23.5% and 26.5% to 34.5%).
- 4.8%, 4.6%, 4.5%, 4.2%, 3.3% and 2.8% of persons under follow-up on 1/1/2010-2015 (respectively) experience a liver-related event.
- The proportion reporting testing HCV positive recently (< 5 years) was low, and significantly differed between regions ($p < 0.0001$), as did the median duration of HCV infection, 14 and 7 years in Southern/Eastern Europe respectively ($p < 0.0001$); 15% of those testing positive recently had fibrosis $\geq F3$.
- After adjustment, non-MSM individuals had higher odds of fibrosis $\geq F3$ compared to MSM, as did individuals aged > 50 compared to those aged 30-40. Compared to Southern Europe, all regions had lower odds of fibrosis $\geq F3$, as did those with CD4 count $> 200/\text{mm}^3$ (**Figure 2**).
- The change over time in fibrosis $\geq F3$ differed between regions ($p = 0.025$). After adjustment, the odds of fibrosis $\geq F3$ was increasing in Southern Europe over time and showed an early increase before 2014-2015 in Northern Europe, with few changes over time in other regions (**Figure 3**).

LIMITATIONS:

- Not every individual had information on the date they were diagnosed, therefore detailed analysis of late presenters was not feasible.
- The proportion of patients with a liver-related event was also small, which precluded regional comparisons.

CONCLUSIONS:

26% of individuals with HIV/HCV had fibrosis $\geq F3$, with significant differences between regions likely attributable to duration of HCV infection. The odds of developing fibrosis $\geq F3$ was increasing by a small amount each year, with the most marked increases in Southern Europe. Although recent HCV diagnoses were uncommon, there was still a considerable proportion of recently diagnosed individuals with fibrosis $\geq F3$. The prevalence of fibrosis $\geq F3$ and the relationship between CD4 and fibrosis $\geq F3$ highlights the need to prioritise HIV and HCV screening, linkage to care and treatment across Europe. If for any reason HCV cannot be treated, the relationship between CD4 count and fibrosis $\geq F3$ also highlights the importance of encouraging patients to start ART while waiting for HCV treatment, to maintain HIV suppressions and increase their CD4 cell count.

Table 1
Characteristics of HIV/HCV co-infected persons, by level of fibrosis

Region of Europe	Overall total N=3712	Fibrosis		
		<F3 N=2747	F3 N=965	>F3 N=100
South	1148 (30.9)	728 (26.5)	420 (43.5)	420 (43.5)
Central - West	768 (20.7)	596 (21.7)	172 (17.8)	172 (17.8)
North	595 (16.0)	429 (15.6)	166 (17.2)	166 (17.2)
Central - East	579 (15.6)	464 (16.9)	115 (11.9)	115 (11.9)
East	622 (16.8)	530 (19.3)	92 (9.5)	92 (9.5)
Age group				
<30	402 (10.8)	359 (13.1)	43 (4.5)	43 (4.5)
30-40	1057 (28.5)	840 (30.6)	217 (22.5)	217 (22.5)
40-50	1292 (34.8)	893 (32.5)	399 (41.3)	399 (41.3)
>50	961 (25.9)	655 (23.8)	306 (31.7)	306 (31.7)
*CD4 count (cells/mm ³)				
<200	572 (15.4)	329 (12.0)	243 (25.2)	243 (25.2)
>200	3046 (82.1)	2353 (85.7)	693 (71.8)	693 (71.8)
*HIV-RNA (cp/ml)				
<500	2986 (80.4)	2258 (82.2)	728 (75.4)	728 (75.4)
500-10000	255 (6.9)	180 (6.6)	75 (7.8)	75 (7.8)
>10000	387 (10.4)	262 (9.5)	125 (13.0)	125 (13.0)
Hepatitis C risk group				
MSM*	519 (14.0)	416 (15.1)	103 (10.7)	103 (10.7)
non-MSM	3193 (86.0)	2331 (84.9)	862 (89.3)	862 (89.3)
*Hepatitis B coinfected				
No	2906 (78.3)	2172 (79.1)	734 (76.1)	734 (76.1)
Yes	142 (3.8)	93 (3.5)	49 (5.1)	49 (5.1)
Gender				
Male	2650 (71.4)	1909 (69.5)	741 (76.8)	741 (76.8)
Female	1062 (28.6)	838 (30.5)	224 (23.2)	224 (23.2)
*cART				
No	189 (5.1)	153 (5.6)	36 (3.7)	36 (3.7)
Yes	3523 (94.9)	2594 (94.4)	929 (96.3)	929 (96.3)
*AIDS				
No	2718 (73.2)	2044 (74.4)	674 (69.8)	674 (69.8)
Yes	994 (26.8)	703 (25.6)	291 (30.2)	291 (30.2)
*HCV-RNA (IU/ml)				
<500,000	1337 (36.0)	1015 (36.9)	322 (33.4)	322 (33.4)
>500,000	2154 (58.0)	1558 (56.7)	596 (61.8)	596 (61.8)

*Characteristics measured prior to fibrosis result for those with fibrosis $\geq F3$, or at last follow-up visits for those with fibrosis $< F3$

*Men Who Have Sex With Men

Figure 1
Regional difference in advanced fibrosis and cirrhosis over time

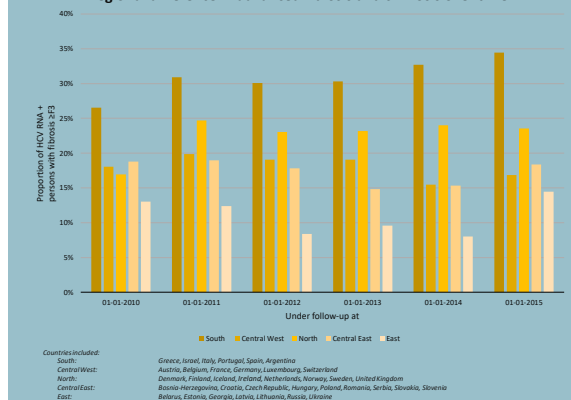


Figure 2
Adjusted* odds ratio of having fibrosis $\geq F3$

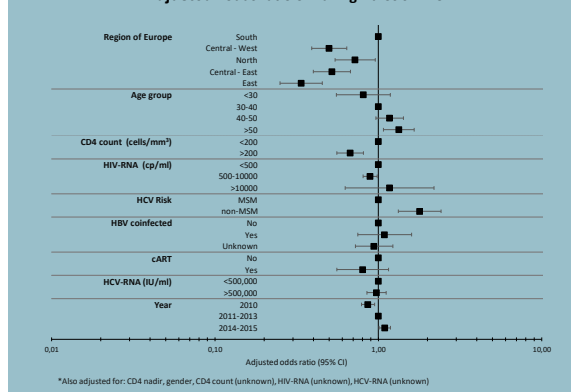
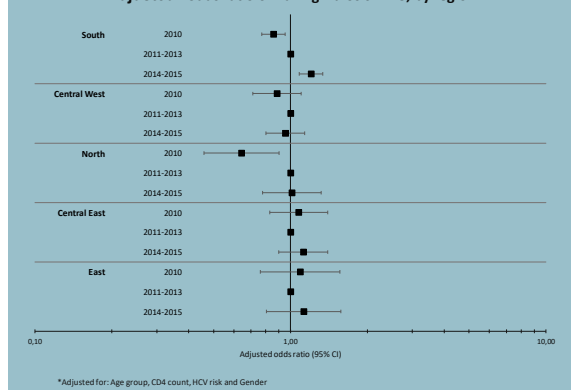


Figure 3
Adjusted* odds ratio of having fibrosis $\geq F3$, by region



*Adjusted for: Age group, CD4 count, HCV risk and Gender