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Liver-related death among HIV/HCV coinfected individuals, implications for the era of directly acting antivirals

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INTRODUCTION

The arrival of potent and less toxic directly acting antivirals (DAA) for treatment of HCV infection may see improved outcomes and less toxicity among HIV coinfected patients. However, the estimated costs of €30,000-90,000 per treatment and lack of sufficient data on adverse events will necessitate prioritisation of those at greatest risk of liver-related death (LRD) for therapy.

A better understanding of the spectrum of causes of death among HIV/HCV coinfected individuals and factors that affect progression to LRD along with potential competing risks is essential in determining who to prioritise for treatment of HCV infection.

This study aims to provide guidance on who should be prioritised for treatment of HCV infection with DAAs.

METHODS

HCVAb positive EuroSIDA patients with follow-up after 1/1/2000 were included with causes of death classified using CoDe methodology. Crude death rates were calculated for LRD, AIDS-related and non-LRD/non-AIDS-related death stratified by patient characteristics. Competing risks Kaplan-Meier (KM) estimation was used to estimate 5-year probabilities of LRD and competing risks Cox proportional hazards models, using the Fine and Gray method, were used to describe factors associated with LRD and non-LRD.

A combination of liver biopsy, Fibroscan®, the biomarker hyaluronic acid and the APRI score were used to define significant fibrosis (Metavir ≥F2).

RESULTS (BASELINE CHARACTERISTICS – TABLE 1)

- 470 deaths with known causes were recorded from 4202 coinfected patients during 23621 PYFU to June 2012. Individuals included were mostly male (68%) injecting drug users (69%).
- Data on HCV-RNA and levels of liver fibrosis were scarce at baseline, however, over the course of follow-up 68% had HCV-RNA determined while 82% had fibrosis data available, with 21% reporting ≥F2 fibrosis.

RESULTS (CRUDE DEATH RATES – TABLE 2)

- The rate of LRD peaked in those aged 35-40. In comparison, rates of AIDS-related and non-LRD/non-AIDS-related death peak in later life.
- LRD rates do not increase in later life as the risk of dying from a competing risk increases.
- LRD rates were far higher among those with low CD4 cell counts and LRD occurred almost exclusively among those with ≥F2 liver fibrosis.

RESULTS (KM ESTIMATED TIME TO LRD – FIGURE 1)

- The 5-year probability of LRD was negligible in those with <F2 liver fibrosis; 0.6% (95% CI: 0.3% – 1.1%) in those with baseline CD4 ≥200cells/mm³ and 0.8% (0.2% – 2.5%) in those with baseline CD4 <200cells/mm³.

Table 1

Baseline characteristics overall and by clinical endpoint

Median (IQR) / %		All (N=4204)	Causes of death: LRD (N=126)	Causes of death: AIDS (N=129)	Causes of death: Non-LRD/Non-AIDS (N=215)	P-Value
Age		36 (30 - 41)	38 (35 - 42)	36 (31 - 41)	38 (34 - 44)	0.0016
Male		2852 (67.8)	90 (71.4)	94 (72.9)	170 (79.1)	0.2155
White		3941 (93.7)	118 (93.7)	125 (96.9)	205 (95.3)	0.4704
Region of EuroSIDA	South	1068 (25.4)	38 (30.2)	28 (21.7)	48 (22.3)	<.0001
	West Central	598 (14.2)	28 (22.2)	9 (7.0)	27 (12.6)	
	North	496 (11.8)	36 (28.6)	23 (17.8)	69 (32.1)	
	East Central	592 (14.1)	9 (7.1)	7 (5.4)	31 (14.4)	
	East	1339 (31.9)	13 (10.3)	56 (43.4)	35 (16.3)	
	Argentina	111 (2.6)	2 (1.6)	6 (4.7)	5 (2.3)	
HIV transmission route	MSM	396 (9.4)	7 (5.6)	8 (6.2)	18 (8.4)	0.3141
	IDU	2905 (69.1)	97 (77.0)	99 (76.7)	165 (76.7)	
	Heterosexual	658 (15.7)	9 (7.1)	16 (12.4)	21 (9.8)	
HCV-RNA status	Negative	362 (8.6)	8 (6.3)	13 (10.1)	27 (12.6)	0.0001
	Positive	1606 (38.2)	71 (56.3)	37 (28.7)	94 (43.7)	
	Unknown	2236 (53.2)	47 (37.3)	79 (61.2)	94 (43.7)	
Duration of HCV infection	Years	3.8 (0.8 – 6.2)	1.6 (0.0 – 4.7)	3.5 (0.8 – 5.3)	1.5 (0.0 – 4.2)	0.0015
HCV genotype	G1	1018 (24.2)	44 (34.9)	20 (15.5)	54 (25.1)	0.0005
	G2	58 (1.4)	2 (1.6)	3 (2.3)	3 (1.4)	
	G3	594 (14.1)	19 (15.1)	12 (9.3)	43 (20.0)	
	G4	286 (6.8)	8 (6.3)	4 (3.1)	11 (5.1)	
HBsAg status	Negative	3450 (82.1)	99 (78.6)	105 (81.4)	179 (83.3)	0.3052
	Positive	312 (7.4)	19 (15.1)	15 (11.6)	17 (7.9)	
CD4 cell count	Cell/mm³	375 (230 - 550)	274 (149 - 461)	207 (90 - 348)	317 (197 - 510)	<.0001
HIV RNA	Log_{10} copies/ml	2.49 (1.69 - 3.94)	2.75 (1.69 - 4.30)	4.24 (2.99 - 5.13)	2.65 (1.69 - 3.99)	<.0001
Liver fibrosis	<F2	1186 (28.2)	10 (7.9)	12 (9.3)	39 (18.1)	0.0034
	≥F2	233 (5.5)	12 (9.5)	4 (3.1)	8 (3.7)	
	Unknown	2785 (66.2)	104 (82.5)	113 (87.6)	168 (78.1)	

Baseline is defined as enrolment into EuroSIDA, the date of HCV coinfection or 1/1/2000, whichever occurred later. Duration of HCV infection is calculated from first documented HCVAb or HCV RNA positive test.
At baseline 5.8% were in the *other* HIV transmission route; 53.5% had unknown HCV genotype; 10.5% had unknown HBsAg status

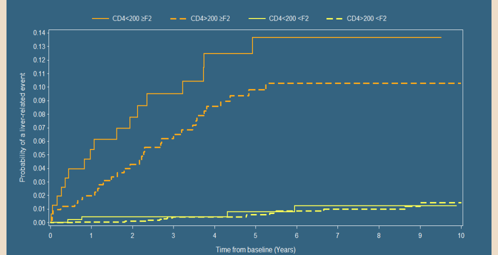
Table 2

Crude death rates per 1000 person years follow-up

Rate (95% C.I.)	Overall (N=470)	Cause of death: Liver-related (N=126)	Cause of death: AIDS (N=129)	Cause of death: Non-LRD/Non-AIDS (N=215)
Age				
< 35	18.2 (14.9 - 21.6)	2.0 (0.9 - 3.1)	6.8 (4.7 - 8.9)	7.3 (5.1 - 9.4)
35 - 45	24.4 (21.4 - 27.3)	7.2 (5.6 - 8.8)	5.3 (3.9 - 6.7)	8.2 (6.5 - 9.9)
45 - 55	22.2 (18.5 - 25.8)	5.5 (3.7 - 7.3)	3.9 (2.3 - 5.4)	9.5 (7.1 - 12.0)
55 - 65	38.9 (26.9 - 50.8)	4.0 (0.1 - 7.9)	7.0 (1.8 - 12.1)	22.9 (13.7 - 32.2)
> 65	39.4 (12.7 - 66.2)	4.9 (0.0 - 14.6)	9.9 (0.0 - 23.5)	19.7 (0.6 - 38.9)
Region of EuroSIDA				
South	17.3 (14.4 - 20.3)	5.1 (3.5 - 6.7)	3.7 (2.4 - 5.1)	6.4 (4.6 - 8.2)
West Central	19.6 (15.3 - 23.9)	7.0 (4.4 - 9.6)	2.3 (0.8 - 3.7)	6.8 (4.2 - 9.3)
North	50.5 (42.8 - 58.2)	11.7 (7.9 - 15.4)	7.4 (4.4 - 10.5)	22.3 (17.1 - 27.5)
East Central	13.9 (10.2 - 17.7)	2.4 (0.8 - 4.0)	1.9 (0.5 - 3.3)	8.3 (5.4 - 11.2)
East	24.0 (19.7 - 28.2)	2.6 (1.2 - 4.1)	11.4 (8.4 - 14.3)	7.1 (4.8 - 9.5)
Argentina	22.8 (10.5 - 35.0)	3.5 (0.0 - 8.3)	10.5 (2.1 - 18.9)	8.8 (1.1 - 16.4)
HCV Status				
Resolved Infection	17.6 (13.2 - 22.1)	3.2 (1.3 - 5.1)	4.4 (2.2 - 6.6)	7.9 (5.0 - 10.9)
Chronic Infection	22.7 (20.2 - 25.2)	6.2 (4.9 - 7.5)	3.4 (2.4 - 4.4)	9.8 (8.2 - 11.5)
Unknown Viremia	26.2 (22.3 - 30.0)	4.5 (2.9 - 6.1)	10.0 (7.6 - 12.4)	7.9 (5.8 - 10.1)
Transmission Risk Group				
MSM	19.5 (13.4 - 25.7)	3.6 (0.9 - 6.3)	4.1 (1.3 - 7.0)	9.2 (5.0 - 13.5)
IDU	24.6 (22.3 - 26.9)	5.6 (4.5 - 6.7)	5.7 (4.6 - 6.9)	9.6 (8.1 - 11.0)
CD4 Cell Count				
< 200	83.0 (73.3 - 92.6)	21.6 (16.5 - 26.7)	29.6 (23.7 - 35.5)	23.5 (18.2 - 28.8)
200 - 350	22.6 (18.6 - 26.6)	5.8 (3.8 - 7.8)	3.6 (2.0 - 5.1)	9.5 (6.9 - 12.1)
350 - 500	10.7 (8.0 - 13.4)	1.9 (0.8 - 3.1)	1.1 (0.2 - 1.9)	6.3 (4.3 - 8.4)
> 500	9.3 (7.4 - 11.3)	1.4 (0.6 - 2.1)	0.4 (0.0 - 0.8)	5.1 (3.7 - 6.5)
Liver Fibrosis				
< F2	10.8 (8.9 - 12.7)	0.5 (0.1 - 0.8)	3.2 (2.1 - 4.2)	5.8 (4.4 - 7.2)
≥ F2	46.3 (37.9 - 54.7)	19.6 (14.1 - 25.2)	6.3 (3.1 - 9.4)	16.7 (11.6 - 21.8)
Unknown	30.6 (27.3 - 33.9)	7.1 (5.5 - 8.8)	7.6 (5.9 - 9.3)	10.7 (8.7 - 12.7)

Figure 1

Kaplan-Meier plot of time to LRD stratified by baseline CD4 and liver fibrosis



N under follow-up for CD4 <200 ≥F2, CD4 >200 ≥F2, CD4 <200 <F2 and CD4 >200 <F2, respectively

163	73	32
441	198	60
524	244	95
2250	1122	344

Log-rank test for strata separation: P<0.0001

- Among those with ≥F2 fibrosis 5-year probabilities of LRD were substantial; 9.2% (6.5% – 12.9%) in those with baseline CD4 ≥200cells/mm³ and 12.3% (7.6% – 19.5%) in those with baseline CD4 <200cells/mm³ (P<0.0001).

RESULTS (FACTORS ASSOCIATED WITH LRD AND NON-LRD – FIGURES 2 AND 3)

- In adjusted Cox models age did not predict LRD, however, duration of HCV coinfection did (adjusted sub-hazard ratio (sHR): 1.43 (95% CI: 1.03 – 1.98; P=0.035) per 5 years longer).
- Significant fibrosis was by far the greatest risk factor for progression to LRD (sHR: 28.4 (13.4 – 60.3; P<0.0001) ≥F2 fibrosis vs. <F2 fibrosis).
- LRD was also associated with viremic HCV coinfection (sHR: 2.40 (1.12 – 5.14; P=0.024) vs. resolved infection) and additional coinfection by HBV (sHR: 6.57 (1.48 – 29.2; P=0.013) vs. HBsAg negative).
- CD4 cell count was an important predictor of both LRD and non-LRD (sHR: 0.61 (0.54 – 0.70; P<0.0001) and 0.65 (0.60 – 0.71; P<0.0001) per doubling, respectively).
- Non-LRD was associated with older age and EuroSIDA regions outside West Central.
- Interestingly, duration of HCV infection (sHR: 1.34 (1.08 – 1.67; P=0.0085) per 5 years) and viremic HCV (sHR: 1.54 (1.05 – 2.24; P=0.026) vs. resolved infection) were also predictors of non-LRD.

CONCLUSIONS

LRD accounted for 27% of all deaths in HIV/HCV coinfected patients in EuroSIDA, on par with AIDS as the leading cause of death. The rate of LRD peaked between the ages 35-45 and was highest in the West Central and North regions. LRD occurred almost exclusively among those with significant liver fibrosis (Metavir ≥F2) and HCV treatment with DAAs should be prioritised for this group.

In Eastern Europe, where the prevalence of HCV coinfection is highest, the rate of LRD remains low with causes of death dominated by AIDS and non-LRD.

In adjusted analysis, risk factors for LRD were low CD4 cell count, detectable HIV RNA and HBsAg positivity. Therefore, early initiation of ART that, in the case of HBV coinfection includes potent HBV active treatment, should be viewed as an important component in a comprehensive strategy to decrease the risk of LRD and the need for expensive HCV treatment among HIV/HCV coinfected patients.

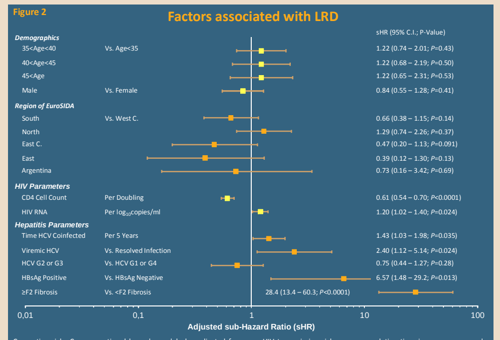
HCV infection may be predictive of non-LRD due to lifestyle factors associated with coinfection with HIV, alternatively it may suggest an inflammatory effect of chronic HCV infection.

LIMITATIONS

The main limitation of this study is that due to limited power we are not able to assess the comparative impact of F1, F2, F3 and F4 fibrosis on mortality. Further, with fibrosis levels determined from multiple data sources, consensus on these definitions is difficult to attain.

Figure 2

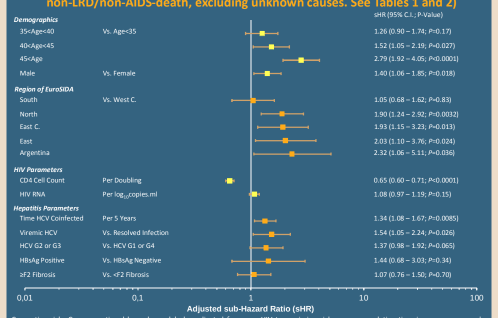
Factors associated with LRD



Competing risks Cox proportional hazards model also adjusted for: race, HIV transmission risk group, cumulative time immunosuppressed (<200 cells/mm²), current cART use, alanine transaminase, baseline calendar year and unknown HCV viremia, HBsAg status and fibrosis status

Figure 3

Factors associated with non-LRD (AIDS-related-death and non-LRD/non-AIDS-death, excluding unknown causes. See Tables 1 and 2)



Competing risks Cox proportional hazards model also adjusted for: race, HIV transmission risk group, cumulative time immunosuppressed (<200 cells/mm²), current cART use, alanine transaminase, baseline calendar year and unknown HCV viremia, HBsAg status and fibrosis status

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