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Short-term Risk of Decompensation Among HIV/HCV-coinfected Individuals with Significant Fibrosis

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ABSTRACT

BACKGROUND: Newer directly acting antivirals against (DAA) HCV are becoming available. Their efficacy and safety profile is better than that of telaprevir or boceprevir. However, newer DAAs are very expensive. The issue is whether to treat now with the available options or to defer therapy until all-oral combinations become less expensive and widely accessible. This management decision may be aided establishing the risk of liver decompensations (DC) and mortality among HIV/HCV-coinfected individuals.
OBJECTIVE: To evaluate the risk of DC and death among HIV/HCV-coinfected individuals according to their baseline fibrosis classified by either liver biopsy (LB) or liver stiffness measurement (LSM).
METHODOLOGY: HIV/HCV-coinfected patients, naïve or without sustained viral response to HCV therapy, prospectively followed (1990-2013), were included in this cohort study. Fibrosis was classified by LB in 683 patients and by LSM in 1046 individuals. Survival analyses were carried out.
RESULTS: For patients with LB, the adjusted subhazard ratio for DC [ASHR, 95% confidence interval (95% CI) by fibrosis stage was: Stage 0, reference category; Stage 1; 2.7 (0.31-23.8), p=0.368; Stage 2, 4.3 (0.47-38.7), p=0.198; Stage 3, 5.98 (0.68-52.5), p=0.106; Stage 4, 15.5 (1.8-134.2), p=0.013. For patients with LSM, the ASHR (95% CI) for DC by LSM category was: <6 KPa, reference category; 6-9.4 KPa; 1.7 (0.16-18.9), p=0.659; 9.5-14.5 KPa; 6.32 (0.71-56.2), p=0.098; ≥14.6 KPa; 52.7 (7.31-379.6), p<0.0001. Regarding the risk of death, the adjusted hazard ratio [AHR (96% CI) for death by fibrosis stage in the LB was: Stage 0, reference category; Stage 1, 1.3 (0.4-4.17), p=0.667; Stage 2, 2.64 (0.84-8.32), p= 0.097; Stage 3, 2.6 (0.82-8.2), p=0.104; Stage 4, 4.84 (1.58-14.8), p=0.006. For patients with LSM, the AHR (95% CI) for death by LSM was: ≤6 KPa, reference category; 6-9.4 KPa, 1.7 (0.61-4.65), p=0.315; 9.5-14.5 KPa, 3.33 (1.19-9.36), p=0.022; ≥14.6 KPa, 12.8 (4.89-33.6), p<0.0001.
CONCLUSIONS: HIV/HCV-coinfected patients without advanced fibrosis are at a low risk of DC in the short-term. However, individuals with fibrosis stage 2 by LB showed a trend for a higher risk of DC and death than those with stage 0.

(Updated abstract)

BACKGROUND

A new generation of direct acting antiviral drugs against HCV (DAA) is becoming available. They have a higher antiviral activity, a lower potential for drug-drug interactions with antiretroviral drugs and a better safety profile than those of telaprevir or boceprevir. In addition, some of these new DAA can be combined in highly effective interferon-free regimens, more convenient and of shorter duration than regimens including boceprevir or telaprevir. The downside of these newer DAAs is their elevated cost, which may limit the accessibility to them. In a few years, the cost of DAAs might decrease as more of them become marketed. Thus, the dilemma for clinicians and health providers is whether to treat now with the available options or to defer therapy until all-oral combinations become less expensive and widely accessible. A rational way to solve this problem is to establish the risk of liver-related events and mortality among HIV/HCV-coinfected individuals without therapy or without response to a previous treatment against HCV. Given that the most important factor driving the outcome of HCV infection is liver fibrosis, the short-term likelihood of liver decompensation by baseline fibrosis stage could be used to make informed therapy decisions.

OBJECTIVE

To assess the risk of liver decompensations (DC) or death among HIV/HCV-coinfected individuals according to their baseline fibrosis classified by either liver biopsy or liver stiffness measurement (LSM).

PATIENTS AND METHODS

- Design: Cohort study (November 1990-May 2013).
- Inclusion criteria:
  - HIV-infected patients with HCV infection as determined by detectable plasma HCV RNA
  - No therapy against HCV infection during their follow-up or no SVR to treatment for HCV infection.
  - Evaluation of fibrosis either by liver biopsy or by LSM.
- Fibrosis classification:
  - Liver biopsy: Staging by the Scheuer index: Stage 0 to stage 4.
  - LSM: Measured by hepatic transient elastography (FibroScan®, Echosens, Paris). Cut-offs applied:
    - LSM ≤6 KPa, minimal or absent fibrosis.
    - LSM ≥9.5 KPa, fibrosis stage 3 or precirrhosis.
    - ≥14.6 KPa, cirrhosis
- Statistical analysis:
  - Primary end-points: Development of the first decompensation of cirrhosis and overall death.
  - Baseline date: The date of inclusion in the cohort was the day corresponding to the evaluation of fibrosis by liver biopsy or LSM.
  - Survival analysis: Factors with a univariate p value ≤0.2 were included in multivariate models adjusted for age, gender and HCV therapy. For DC, deaths due to AIDS or other causes not attributable to liver failure were considered competing events.

RESULTS

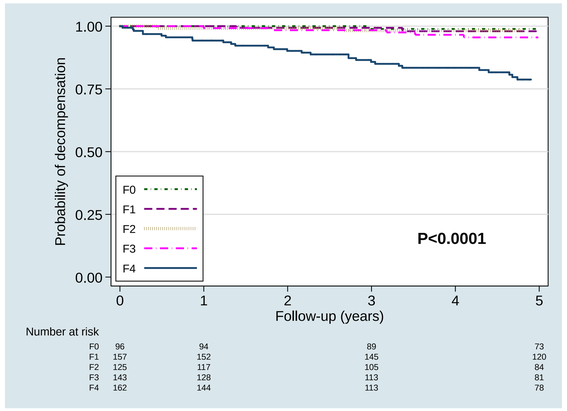
Patients classified using liver biopsy

Characteristics of the patients (n=683)

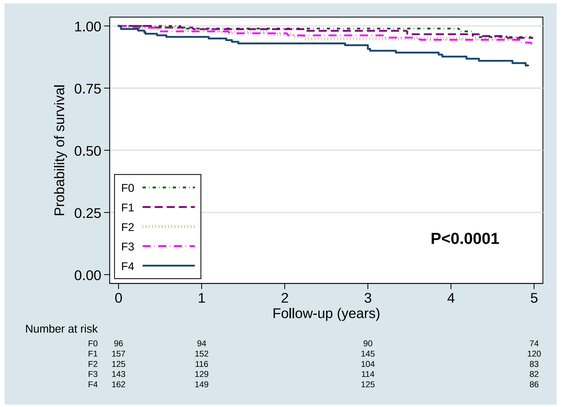
Characteristic	
Age[1], years	45 (41-49)
Male gender, n (%)	556 (81)
Previous use of injecting drugs, n (%)	594 (87)
Baseline CD4 cell counts[1], cells/mL	479 (321-653)
Baseline HIV RNA<50 copies/mL, n (%)	499 (73)
Antiretroviral therapy at baseline, n (%)	628 (92)
Clinical AIDS, n (%)	239 (35)
HCV genotype[2], n (%)	
1	413 (64)
2	7 (1.1)
3	105 (16)
4	118 (18)
HBs Ag positive, n (%)	17 (2.5)
Treatment against HCV, n (%)	311 (46)
Null response[3], n (%)	183 (59)
Relapse after treatment[3], n (%)	61 (20)
Fibrosis stage, n (%)	
Stage 0	96 (14)
Stage 1	157 (23)
Stage 2	125 (18)
Stage 3	143 (21)
Stage 4	162 (24)

1: Median (IQR); 2: Not available in 40 (5.9%) patients; 3: Applicable to 311 patients who received treatment against HCV.

Probability of the first liver decompensation according to liver fibrosis stage



Survival according to liver fibrosis stage



Risk of liver decompensation according to fibrosis stage

Fibrosis	Unadjusted SHR[1] (95% CI[2])	Univariate p	Adjusted SHR[1] (95% CI[2])	Multivariate p
Stage 0	Reference	-	Reference	-
Stage 1	3.9 (0.46-32.8)	0.210	2.7 (0.31-23.8)	0.368
Stage 2	6.82 (0.89-54.8)	0.071	4.3 (0.47-38.7)	0.198
Stage 3	8.86 (1.13-69.5)	0.038	5.98 (0.68-52.5)	0.106
Stage 4	30.5 (1.5-92.5)	0.001	15.5 (1.8-134.2)	0.013

Competing risks regression model adjusted by age, gender and platelet counts at baseline, and treatment against HCV.
1. SHR: Subhazard ratio; 2. 95% CI: 95% confidence interval.

Risk of death according to fibrosis stage

Fibrosis	Unadjusted HR[1] (95% CI[2])	Univariate p	Adjusted HR[1] (95% CI[2])	Multivariate p
Stage 0	Reference	-	Reference	-
Stage 1	1.3 (0.44-3.81)	0.637	1.3 (0.4-4.17)	0.667
Stage 2	2.47 (0.88-6.89)	0.085	2.64 (0.84-8.32)	0.097
Stage 3	2.44 (0.88-6.75)	0.086	2.6 (0.82-8.2)	0.104
Stage 4	5.34 (2.08-13.68)	<0.0001	4.84 (1.58-14.8)	0.006

Cox regression models adjusted by age, gender, platelet counts, AIDS, CD4 cell counts, undetectable HIV RNA at baseline and treatment against HCV.
1. HR: Hazard ratio; 2. 95% CI: 95% confidence interval.

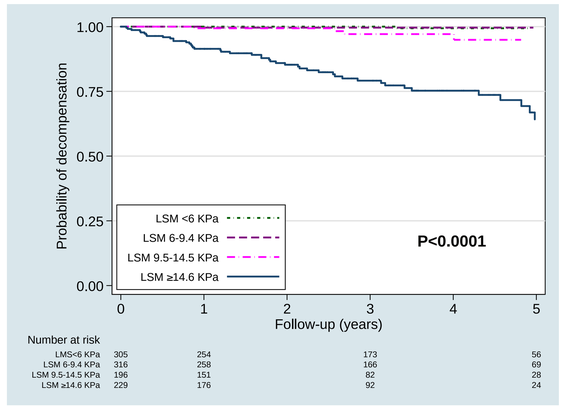
Patients classified using liver stiffness measurement

Characteristics of the patients (n=1042)

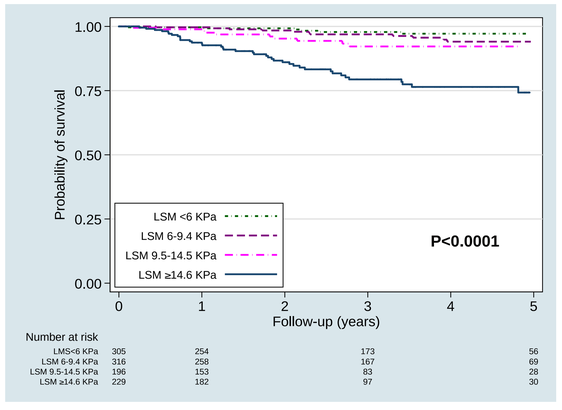
Characteristic	
Age[1], years	43 (40-47)
Male gender, n (%)	865 (83)
Previous use of injecting drugs, n (%)	911 (87)
Baseline CD4 cell counts[1], cells/mL	433 (274-639)
Baseline HIV RNA <50 copies/mL, n (%)	705 (67)
Antiretroviral therapy at baseline, n (%)	897 (86)
Clinical AIDS, n (%)	374 (36)
HCV genotype[2], n (%)	
1	583 (64)
2	12 (0.1)
3	132 (14)
4	184 (20)
HBs Ag positive, n (%)	19 (1.8)
Treatment against HCV, n (%)	305 (29)
Null response[3], n (%)	200 (67)
Relapse after treatment[3], n (%)	48 (16)
LSM[1], KPa	7.9 (5.8-13.1)
LSM categories, n (%)	
<6 KPa	305 (29)
6-9.4 KPa	316 (30)
9.5-14.5 KPa	196 (19)
≥14.6 KPa	229 (22)

1: Median (IQR); 2: Not available in 135 (13%) patients; 3: Applicable to 305 patients who received treatment against HCV.

Probability of the first liver decompensation according to liver stiffness measurement



Survival according to liver stiffness measurement



Risk of liver decompensation according to liver stiffness measurement

LSM	Unadjusted SHR[1] (95% CI[2])	Univariate p	Adjusted SHR[1] (95% CI[2])	Multivariate p
<6 KPa	Reference	-	Reference	-
6-9.4 KPa	0.97 (0.06-15.1)	0.981	1.7 (0.16-18.9)	0.659
9.5-14.5 KPa	7.6 (0.85-67.8)	0.069	6.32 (0.71-56.2)	0.098
≥14.6 KPa	75.87 (10.54-546)	<0.0001	52.7 (7.31-379.6)	<0.0001

Competing risks regression model adjusted by age, gender, platelet counts, CD4 cell counts and AIDS at baseline, and treatment against HCV.
1. SHR: Subhazard ratio; 2. 95% CI: 95% confidence interval.

Risk of death according to fibrosis stage

LSM	Unadjusted HR[1] (95% CI[2])	Univariate p	Adjusted HR[1] (95% CI[2])	Multivariate p
<6 KPa	Reference	-	Reference	-
6-9.4 KPa	1.8 (0.67-4.92)	0.238	1.7 (0.61-4.65)	0.315
9.5-14.5 KPa	3.15 (1.15-8.69)	0.026	3.33 (1.19-9.36)	0.022
≥14.6 KPa	11.2 (4.75-26.4)	<0.0001	12.8 (4.89-33.6)	<0.0001

Cox regression models adjusted by age, gender, platelet counts, AIDS, CD4 cell counts, undetectable HIV RNA at baseline and treatment against HCV.
1. HR: Hazard ratio; 2. 95% CI: 95% confidence interval.

CONCLUSIONS

HIV/HCV-coinfected patients without advanced fibrosis are at a low risk of decompensation in the short-term. However, individuals with fibrosis stage 2 by biopsy showed a trend for a higher risk of decompensation and death than those without fibrosis.

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