Progression of liver fibrosis among HIV-infected patients under suppressive antiretroviral therapy: role of untreated HCV and other unrelated factors in the ICONA Foundation study cohort

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Background

- In several countries (including Italy), HCV treatment is currently available only for those with the greatest need, that is patients with liver cirrhosis or significant fibrosis.
- HCV/HIV-coinfected patients has been associated with faster liver fibrosis progression than HCV–monoinfection.
- Although mitigated by suppressed antiretroviral therapy, this faster progression seems to persist also when HCV viral replication is under control.

Objectives

- Identifying predictors of faster liver fibrosis progression among HIV-infected subjects with significant fibrosis could be crucial for prioritizing interventions (including anti-HCV treatment) in selected patients.
- We aimed at assessing the rate of progression to advanced liver fibrosis among HIV-infected patients on suppressive antiretroviral therapy (ART), with or without HCV-coinfection, and identifying its predictors, in a large cohort of Italian HIV-infected individuals.

Methods

- Patients from the ICONA cohort with two consecutive HCV-RNA<50 copies/ml after ART initiation were enrolled if: HCV-antibody (HCVAb) status was known; ≥2 FIB-4 after HVRNA suppression were available and Baseline FIB-4 was <3.25.
- FIB-4 was calculated according to the following formula:
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  \text{FIB-4} = \frac{\text{AST} \times \text{ULN}}{\text{plaquelets count} \times 10^5} + \frac{\text{ALT}^3}{\text{ULN}}
  \]
- Patients were followed from the first of two consecutive FIB-4<50 copies/ml (baseline) up to the last available FIB-4. HVRNA rebound, or anti-HCV treatment introduction, whichever occurred first.
- Time to development of advanced fibrosis, defined as the first of two consecutive FIB-4>3.25 (study outcome), was assessed using multivariable Cox regression, conducted among HCV-positive and HCV-Ab-negative patients separately.
- The tested covariates were: gender, body mass index, alcohol use, smoking, treatment with ART, or new start of ART (IDU) as HIV risk factor, CD4 nadir, baseline CD4, HDL-cholesterol, diabetes, duration of HIV infection, HCV-RNA, HCV-genotype, baseline FIB-4, first-line ART drugs.

Results

- 5,717 patients with a median follow-up of 4 (IQR 2.2-7.4) years, contributing to 30,399 patient-years of follow-up (PYFU), were included. The median number of FIB-4 measurements was 7 per patient (IQR 4-14). Patients were predominantly 75% (75%), their median age was 40 years (IQR 34-61; 114 patients (20%) were HCV-positive. Median baseline FIB-4 was 1.09 (IQR 0.81-1.58) and 0.81 (IQR 0.59-1.12) among HCV-positive and HCV-negative patients, respectively (Table).
- During the follow-up, 272 patients progressed to advanced HCV fibrosis among HCV-positive patients with positive or unknown HCV-RNA (2.94% [95%CI 2.43-3.55] and 3.10% [95%CI 2.51-3.83] per 100 PYFU, respectively) than among HCV-negative or HCV-positive HCV-RNA-negative patients (0.33 [95%CI 0.26-0.41] and 0.49% [95%CI 0.19-1.32] per 100 PYFU, respectively).

Risk factors for fibrosis progression among HCV-Ab positive patients

- Univariate analysis, conducted using ART-positive patients, showed that male gender (HR 1.73 [95%CI 1.21-2.47], history of IDU (HR 1.7 [95%CI 1.18-2.47], positive or unknown HCV-RNA (versus negative, HR 6.14; 95%CI 2.26-16.66 and HR 6.51; 95%CI 2.39-17.76, higher baseline FIB-4 (per unit increase, HR 3.86; 95%CI 3.22-4.62) and first ART containing d4t or d4l (HR 1.46; 95%CI 1.08-1.97) were associated with a higher risk of progression. Conversely, CD4 nadir >200/mm3 (HR 0.74; 95%CI 0.55-0.97), HDL cholesterol >35 mg/dl (HR 0.6; 95%CI 0.44-0.82) and PIV-1-based first-line therapy (HR 0.65; 95%CI 0.43-0.99) resulted to be protective. No significant impact was exerted by HCV genotype.
- When multivariable survival analysis was run, after adjustment for HCV-RNA, baseline FIB-4 (per unit increase, HR 3.81, 95%CI 3.15-4.60, P<0.001) and didanosine or stavudine use (HR 1.38, 95%CI 1.01-1.89, P=0.040) were confirmed to be associated with a higher risk of fibrosis progression, while HDL cholesterol (> vs ≤35 mg/dl, HR 0.85 95%CI 0.47-0.89, P=0.008) was protective. (Figure)

Risk factors for fibrosis progression among HCV-Ab negative patients

- Among HCV-Ab-negative patients, multivariable analysis showed that higher baseline FIB-4 (per unit increase, HR 3.88, 95%CI 2.86-5.26, P<0.001) and first-line ART containing didanosine or stavudine (HR 1.65, 95%CI 0.99-2.75, P=0.054) were the only factors independently associated with fibrosis progression.

Conclusions

- In our cohort, progression to advanced liver fibrosis was associated, irrespective of HCV sero-status, with drugs-containing ART.
- Although these regimens are no longer used, patients to whom they may have caused irreversible iatrogenic damage, thus contributing to hasten fibrosis progression due to other causes.
- In HCV-coinfected patients, HDL-cholesterol had a protective role on fibrosis progression. Whether it is due to its role in regulating homeostasis and counteracting inflammation and oxidative stress, or HDL levels are rather a marker of severity of liver damage, warrants further investigation.