11° CONGRESSO NAZIONALE
ICAR Italian Conference on AIDS and Antiviral Research
Presidenza del Congresso
Antonella Castagna
Antonella d'Arminio Monforte
Massimo Puoti
Giuliano Rizzardini
Promosso da SIMIT Società Italiana di Malattie Infettive e Tropicali
5-7 GIUGNO 2019
UNIVERSITÀ DEGLI STUDI DI MILANO
PD38
Italian Cohort Naive Antiretrovirals I.C.O.N.A.
Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS
Conceived by Professor Mauro Moroni

Serious liver events and liver-related deaths in HIV/HCV co-infected patients with diabetes: data from the ICONA Foundation Cohort Study

S. Leone1, P. Lorenzini2, A. Cozzi-Lepri3, G. Orofino4, D. Bernacchia5, A. Castagna6, M. Menozzi7, G. Guaraldi7, G. Madeddu8, A. Di Biagio9, A. Gori10, A. d'Arminio Monforte11 for the ICONA Foundation Study Group.

1Division of Infectious Diseases, Department of Internal Medicine, San Giuseppe Moscati Hospital, Avellino, Italy; 2 INMI L. Spallanzani, Rome, Italy; 3 Institute for Global Health, University College London, London, UK; 4Infectious Diseases Unit A, Amedeo di Savoia Hospital, Turin, Italy; 5Infectious Diseases Unit, ASST Fatebenefratelli-Sacco, DIBIC 'L. Sacco', University of Milan, Milan, Italy; 6Infectious Diseases Department, IRCCS San Raffaele Scientific Institute & Vita-Salute University, Milan, Italy; 7Clinic of Infectious Diseases, University of Modena and Reggio Emilia, Modena, Italy; 8Infectious Diseases Unit, Department of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy; 9Infectious Diseases Unit, Policlinico San Martino Hospital, Genoa, Italy; 10 Infectious Diseases Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy and Department of Pathophysiology and Transplantation, School of Medicine and Surgery, University of Milan, Milan, Italy; 11Clinic of Infectious and Tropical Diseases, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.

Introduction

-The improvement in AIDS-related survival rates resulted in an increase of non-HIV-related deaths, including liver-related deaths and especially those due to chronic hepatitis C.

-HCV infection seems to be associated with an increased incidence rate of diabetes mellitus, which itself plays a major role in the acceleration of liver disease and in the increased probability of liver-related complications.

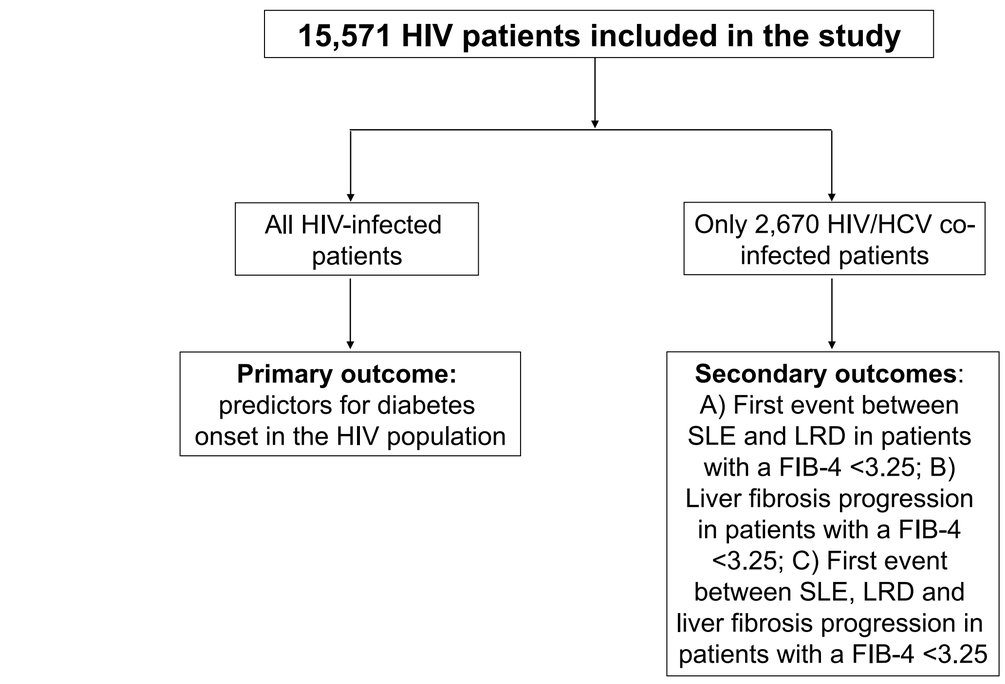
-Glucose abnormalities, including insulin resistance and diabetes, are associated with an increased occurrence of severe liver fibrosis due to increased oxidative stress and inflammatory cytokine secretion.

-The aim of our study was firstly, to investigate the association between diabetes and HCV infection in the HIV population, and, secondly, to determine the risk factors of serious liver events (SLE) and liver-related deaths (LRD) and fibrosis progression among HIV/HCV co-infected patients enrolled in a large Italian cohort.

Methods

Patients were selected from the ICONA. For the purpose of this study, all patients free from SLE at baseline, enrolled since January 1997 up to December 2018 were included if they had at least one follow up visit. Two different analyses were performed: 1) A cross-sectional analysis (Primary outcome) was performed to investigate, in persons living with HIV, the association between diabetes and HCV-Ab and HCV-RNA positivity, by means of multivariable logistic regression. Patients were observed at their last follow up; 2) A longitudinal analysis (Secondary outcomes) was performed in the population of HIV/HCV co-infected patients free from SLE and with FIB-4 index <3.25 at baseline, using the following endpoints: A) first event between SLE and LRD; B) liver fibrosis progression defined as the first of 2 consecutive FIB-4>3.25; C) first event between SLE, LRD and liver fibrosis progression. The baseline of the secondary analysis was the date of first HCV-Ab positivity. Patients were followed until onset of first SLE or LRD or last available clinical follow-up, whichever occurred first. Type 2 diabetes diagnosis was used as time-dependent covariate.

Patients included in the study



Results 1 – Patients' characteristics

We included 15,571 HIV patients, and among these, 2,944 (18.9%) individuals were HCV-Ab positive. The median age was 43 (IQR 36-51) years; 11,927 (76.6%) patients were male; 2,573 (16.5%) patients became HIV-infected through injection drug use (IDU), 5,926 (38.1%) patients were infected through homosexual contact, and 5,981 (38.4%) through heterosexual contact; 754 (4.8%) patients were found to be HBsAg positive. Median (IQR) CD4+ cell count at baseline was 591 (387-820) cells/mmc and median (IQR) HIV-RNA at baseline was 1.6 (0-2.7) $\log_{10}$ copies/ml; 2,136 (13.7%) patients had an AIDS diagnosis at baseline. Almost all of the patients (97.1%) had available baseline FIB-4 index: 11,767 (75.6%) patients had a FIB-4 <1.45, 2,579 (16.6%) patients had an index between 1.45 and 3.25, and 778 (5.0%) patients had a FIB-4 >3.25, respectively.

Results 2 – Diabetes

Over 15,571 HIV-infected patients, 739 (4.7%) presented a diagnosis of diabetes at their last follow-up. Among HIV/HCV co-infected population, 107 patients had a diagnosis of diabetes (29 patients were diabetic at baseline and 78 patients developed diabetes during the follow-up). Viremic HCV co-infection was independently associated with diabetes diagnosis. Other factors independently associated with diabetes diagnosis were older age, higher BMI values, HIV-RNA detectable at baseline, higher FIB-4 score, hypertension, hypercholesterolemia, and hypertriglyceridemia (Table 1).

Table 1

		aOR	95%CI	p value
Age	<45	1.00		
	45-55	1.79	1.43-2.24	0.000
	>55	2.15	1.64-2.82	0.000
BMI	<18.5	1.27	0.72-2.23	0.413
	18.5-24.9	1.00		
	25-29.9	1.68	0.94-3.00	0.081
	≥30	4.93	2.71-8.98	0.000
HIV-RNA at BL, cp/ml	Not detected	1.00		
	≤50 detected	3.08	2.25-4.22	0.000
	>50 detected	5.79	4.17-8.03	0.000
HCV-Ab & HCV-RNA	HCV-Ab negative	1.00		
	HCV-Ab +ve and HCV-RNA -ve	0.59	0.33-1.09	0.091
	HCV-Ab +ve and HCV-RNA +ve	3.35	2.38-4.71	0.000
	HCV-Ab +ve and HCV-RNA unk	0.67	0.42-1.05	0.082
	HCV-Ab unk	0.47	0.27-0.80	0.005
FIB-4 index	<1.45	1.00		
	1.45-3.25	1.32	1.05-1.65	0.018
	>3.25	1.48	1.07-2.03	0.016
Blood hypertension	No	1.00		
	Yes	2.33	1.83-2.96	0.000
Total cholesterol, mg/dl	≤200	1.00		
	>200	1.29	1.04-1.59	0.018
Triglycerides, mg/dl	≤150	1.00		
	>150	3.66	2.99-4.48	0.000

Results 3 – SLE/LDR and FIB-4 >3.25

2670 HCV-Ab positive subjects with a FIB-4 <3.25 were selected for this analysis and observed for 20,410 PYFU, 85 SLEs/LRDs occurred. The IR was 4.2/1000 PYFU (95%CI 3.4-5.2). We observed 65 SLEs: 19 (29.2%) ascites, 10 (15.4%) hepatic encephalopathy, 9 (13.8%) HCC, 8 (12.3%) gastrointestinal bleeding, 3 (4.6%) hepatorenal syndrome, and 16 (24.6%) hepatic failure not specified; moreover, there were 20 (23.5%) LRDs. Diabetic patients had 3-fold IR of pooled SLE and LRD than patients without diabetes. Diabetes was independently associated with higher risk of SLEs/LRDs. Additional predictors are shown in Table 2. Multivariable analysis showed that HBV co-infection, AIDS diagnosis, viremic HCV co-infection, higher FIB-4 at baseline, and every day alcohol use were independently associated with liver fibrosis progression. Conversely, diabetes was not associated with risk of liver fibrosis progression (Table 2).

Table 2

		SLE/LDR			FIB>3.25		
		aIRR	95%CI	p value	aIRR	95%CI	p value
Diabetes (time-updated)	No	1.00			1.00		
	Yes	3.06	1.30-7.19	0.010	0.94	0.51-1.75	0.848
Gender	Male	1.00			1.00		
	Female	2.05	1.24-3.38	0.005	0.71	0.54-0.92	0.012
HBsAg	Negative	1.00			1.00		
	Positive	5.78	3.17-10.53	0.000	1.75	1.18-2.60	0.005
AIDS diagnosis	No	1.00			1.00		
	Yes	2.27	1.14-4.53	0.020	1.67	1.18-2.35	0.004
HCV-RNA	Negative	1.00			1.00		
	Positive	3.35	1.14-9.83	0.028	2.74	1.71-4.40	0.000
FIB-4 at BL (per 1 point higher)		2.01	1.49-2.71	0.000	2.77	2.42-3.18	0.000
Alcohol use	Abstainers	1.00			1.00		
	Occasionally	0.69	0.14-3.26	0.636	1.68	0.98-2.86	0.058
	Every day	1.99	0.52-7.65	0.319	2.06	1.18-3.59	0.011

Results 4 – aIRR of SLE/LDR/FIB-4 >3.25

Longer HIV history (> 10 years: aIRR 1.34 [95%CI 1.05-1.71], HBV co-infection (aIRR 1.90 [95%CI 1.31-2.76]), AIDS diagnosis (aIRR 1.71 [95%CI 1.22-2.39]), viremic HCV co-infection (aIRR 2.88 [95%CI 1.80-4.62]), higher FIB-4 at baseline (aIRR 2.71 [95%CI 2.38-3.10]), and every day alcohol use (aIRR 2.04 [95%CI 1.19-3.50]), but not diabetes (aIRR 0.92 [95%CI 0.49-1.70]) were independently associated with higher risk of SLE/LRD/FIB-4 >3.25 occurrence.

Conclusions

-We found that HCV infection was associated with a 3-fold increased risk of diabetes onset than uninfected patients. Among HCV-Ab positive patients, we observed that the probability of diabetes occurrence was independently associated with viremic HCV infection. Diabetic patients had a 3-fold increased risk of pooled SLE and LRD than those without diabetes.

-We found that diabetes was not associated with the risk of liver fibrosis progression. These results can be mainly explained by low rate of diabetes diagnosis among our HIV/HCV co-infected patients and high rate of patients who had a baseline a FIB-4 index between 1.45 and 3.25. Indeed, it is well known that FIB-4 index had a lower accuracy for FIB-4 values inside 1.45-3.25 range.

-The major strengths of our study are that it is based on a large cohort of HIV-infected patients with a long follow-up. Furthermore, our study is one between few studies which evaluated the role of diabetes as predictor of SLE and LRD among HIV/HCV co-infected patients. However, our study has also some limitations that need to be taken into account. We have included a small number of patients with diabetes that can explain the lack in power to determine the role of diabetes in the liver fibrosis progression. Finally, a general under-reporting of liver-related complications, as with all observational studies, is possible.

-In conclusion, in our cohort, viremic HCV co-infection is independently associated with diabetes. Furthermore, among HIV/HCV co-infected population, diabetic patients showed an increased risk of SLE/LRD compared to who did not have diabetes. These results warrant further investigations to better characterize the role of diabetes as an independent prognostic factor for liver-related complications among HIV/HCV co-infected patients.