

## **Incidence and Progression to Cirrhosis of New HCV infections in Persons Living with HIV**

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## **Abstract**

### Objective

To estimate the incidence of HCV seroconversion and the risk of severe fibrosis/cirrhosis in HCV seroconverters among persons with HIV.

### Methods

We analyzed data on 4,059 persons with HIV enrolled in a cohort study in Italy .

### Results

Incidence rate of seroconversion was 0.6/100 person-years overall, and drug users and men-who-have-sex-with-men were at highest risk. The cumulative risk of progression to severe fibrosis/cirrhosis was 30% by 10 years after seroconversion.

### Conclusions

New HCV infections have a rapidly progressive course in this population. Persons with HIV and HCV superinfection should be prioritized for treatment with anti-HCV direct-acting antivirals

## Introduction

Liver disease due to hepatitis C virus (HCV) infection is a major cause of morbidity and mortality among persons living with HIV (PLHIV) [1,2], and there is evidence that HIV infection may increase the rate of progression to liver cirrhosis [3]. Studies conducted on small patients series in the context of an increased spread of HCV infection among HIV-infected men-who-have-sex-with-men (MSM) [4-6], suggested that newly acquired HCV infection may lead to rapid progression of fibrosis .

The aim of our analysis was to estimate the incidence and predictors of HCV seroconversion and the risk of progression to cirrhosis in HCV seroconverters PLHIV in Italy.

## Methods

We studied PLHIV enrolled in an observational multicentre cohort study in Italy, the ICONA Foundation Study [7]. Patients included in this analysis were those with an anti-HCV negative test, in whom at least a second anti-HCV test was performed. Individual follow-up accrued from the time of the first HCV-negative test and ended at the time of their first positive or last negative test. We defined the time of occurrence of seroconversion as the mid-point of the time interval between the last negative and the first positive test. We estimated HCV incidence as number of HCV seroconversions observed divided by person-years of follow-up (PYFU). The determinants of seroconversion were analysed by Cox regression model which included gender, mode of HIV transmission, age, clinical stage, HBsAg status, Treponema pallidum serum antibodies and previous sexually transmitted disease at baseline, and the following time-updated covariates: CD4 cells count, plasma HIV-RNA, antiretroviral treatment, and alcohol use. Among HCV seroconverters, we analyzed the progression to severe fibrosis/cirrhosis defined as the occurrence of liver related death, liver decompensation, a clinical diagnosis of cirrhosis or a FIB-4 score  $>3.25$  [8]. We estimated the risk of progression using Kaplan Meier method and we analysed predictors of progression by a Cox regression model including: gender, mode of HIV transmission, age, clinical stage, CD4 cells count, HIV viral load, HBsAg status at seroconversion and time-updated alcohol use.

## Results

Of the 4,059 patients included in the analysis, 1787 (44.0%) were tested twice, 870 (21.4%) were tested 3 times, and 1402 (34.6%) were tested  $\geq 4$  times. Over a total of 28,867 PYFU, 185 seroconversions were recorded; the estimated Incidence Rate (IR) of HCV infection was 0.6 per 100 PYFU (95% confidence intervals [CI] 0.5-0.7).

Incidence rate of HCV seroconversion was highest among injecting drugs users (IDUs) (7.2 per 100 PYFU ; 95% CI 5.4-9.6), followed by MSM (0.7 per 100 PYFU ; 95% CI 0.6-0.9), heterosexual contacts (0.3 per 100

PYFU ; 95% CI 0.2-0.4) . Over time, incidence rates decreased in the overall study population (from 1.6 per 100 PYFU in 1997-2000, to 0.4 in 2013-2016) and among IDUs (from 17.1 per 100 PYFU, in 1997-2000 to 1.0 in 2013-2016) (Figure 1). In contrast the incidence rate was stable in MSM (0.8 per 100 PYFU, in 1997-2000 and 0.8 in 2013-2016).

In multivariable analysis, being IDU ( relative hazard (RH) 19.04, 95% CI 11.63-31.18) or MSM (RH 1.97, 95% CI 1.22-3.19) compared to heterosexuals and positive for Treponema (RH 2.02, 95% CI 1.28-3.18) were associated with a higher risk of seroconversion. Lower risk was associated with older age (RH 0.79 per 10 years older, 95% CI 0.65-0.96) (Supplementary table S1).

Thirty-one patients started a treatment for HCV infection, of whom 27 received interferon-based treatments and 4 direct-acting antivirals (DAAs)-based treatments. Among the 185 seroconverters, 35 developed severe fibrosis/cirrhosis (34 fib4>3.25 and 1 clinical diagnosis of cirrhosis) over 958 PYFU for an estimated rate of 3.6 per 100 PYFU (95%CI 2.6-5.1). Estimated cumulative probability of progression to cirrhosis was 7.4% (95%CI 4.2-12.7) by 2 years, 17.1% (95%CI 11.7-24.6) by 5 years and 29.9% (95%CI 21.5-40.5) by 10 years from seroconversion (Figure 2). In multivariable analysis, IDU as mode of HIV transmission (RH 3.47 95%CI 1.47-10.48) and alcohol use (RH 20.79 95%CI 1.57-274.80) were associated with progression to cirrhosis (supplementary table S2).

## Discussion

The incidence of new HCV infection in our cohort was of the same order of magnitude of that reported in other cohort studies [9,10] . Consistently with previous reports [9,11] we observed a decreasing trend in incidence among IDUs, while, although a non negligible incidence of HCV in MSM was recorded, we did not observe the increasing trend in incidence in these patients that has been reported in other cohorts [10]. Nonetheless, our data suggest a potential usefulness of periodic HCV testing for IDUs and MSM living with HIV.

In a meta-analysis of observational studies on PLHIV with prevalent HCV infection, the predicted cumulative probability of cirrhosis 10 years after the estimated date of HCV infection was 2.3% [3]. In our study we estimated a progression to cirrhosis of 30% 10 years after HCV seroconversion, and this finding is consistent with the hypothesis that among PLHIV the course of HCV infection is worse when it is acquired after HIV, compared to that observed among HCV infected persons who acquire HIV after HCV or at the same time. The risk of progression to cirrhosis in our study was not associated with HIV- related factors such as CD4 cells count and HIV viral load.

This study has some limitations: information on alcohol and recreational drug use was incomplete, the frequency of anti HCV tests was lower than in other studies (12) and the definition of liver disease

progression was mainly based on FIB-4 score, however a recent study suggests that this score is highly predictive of liver related events in HIV-HCV co-infected individuals (13). On the other hand the number of seroconversions that we recorded is larger than that reported in other cohort studies analysed thus far [10]

The advent of DAAs has revolutionized the therapy of HCV infection, since these drugs may cure at least 90% of patients, regardless of the presence of HIV co-infection (14). Nonetheless, the high cost of these drugs has forced health systems, even in resource-rich countries, to adopt rationing policies that have in practice limited the access to these drugs to the sickest patients. Our data, strongly suggest that persons with HIV and HCV superinfection, regardless of the severity of liver disease, should be prioritized for DAAs treatment.

#### **Conflict of interest statement.**

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## Figure legends

**Figure 1** Incidence rates of HCV seroconversion by calendar year and HIV risk factor

**Figure 2** Kaplan Meier Estimate of the probability of progressing to HCV-related severe fibrosis/cirrhosis in Persons Living with HIV with HCV seroconversion in the Icona cohort