



## Research note

Incidence and progression to cirrhosis of new hepatitis C virus infections in persons living with human immunodeficiency virus<sup>☆</sup>

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## ABSTRACT

**Objective:** To estimate the incidence of hepatitis C virus (HCV) seroconversion and the risk of severe fibrosis/cirrhosis in HCV seroconverters among persons with human immunodeficiency virus (HIV) infection.

**Methods:** We analysed data on 4059 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.

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## Introduction

Liver disease due to hepatitis C virus (HCV) infection is a major cause of morbidity and mortality among persons living with human immunodeficiency virus (HIV) [1,2], and there is evidence that HIV infection may increase the rate of progression to liver cirrhosis [3]. Studies conducted on small series of patients 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 among persons living with HIV in Italy.

## Materials and methods

We studied persons living with HIV enrolled in an observational multicentre cohort study in Italy, the ICONA Foundation Study [7]. Patients included in this analysis were those with a negative anti-HCV 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

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as the mid-point of the time interval between the last negative and the first positive tests. 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, hepatitis B surface antigen (HBsAg) status, *Treponema pallidum* serum antibodies and previous sexually transmitted disease at baseline, and the following time-updated covariates: CD4 cell count, plasma HIV RNA, antiretroviral treatment and alcohol use. Among HCV seroconverters, we analysed 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 analysed predictors of progression with a Cox regression model including: gender, mode of HIV transmission, age, clinical stage, CD4 cell count, HIV viral load, HBsAg status at seroconversion and time-updated alcohol use.

## Results

Of the 4059 patients included in the analysis, 1787 (44.0%) were tested twice, 870 (21.4%) were tested three times, and 1402 (34.6%) were tested four or more times. Over a total of 28 867 PYFU, 185 seroconversions were recorded; the estimated Incidence Rate of HCV infection was 0.6 per 100 PYFU (95% CI 0.5–0.7).

Incidence rate of HCV seroconversion was highest among injecting drug 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) (Fig. 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 an IDU (relative hazard (RH) 19.04, 95% CI 11.63–31.18) or MSM (RH 1.97, 95% CI 1.22–3.19) compared with heterosexuals, and being 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) (see Supplementary material, Table S1).

Thirty-one patients started a treatment for HCV infection, of whom 27 received interferon-based treatments and four received

direct-acting antiviral-based treatments. Among the 185 seroconverters, 35 developed severe fibrosis/cirrhosis (34 FIB-4  $>3.25$  and one 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 (Fig. 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 (see Supplementary material, Table S2).

## Discussion

The incidence of new HCV infection in our cohort was of the same order of magnitude as that reported in other cohort studies [9,10]. Consistently with previous reports [9,11] we observed a decreasing trend in incidence among IDUs, whereas, 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 persons living with HIV 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 persons living with HIV the course of HCV infection is worse when it is acquired after HIV, compared with 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, although 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 so far [10].

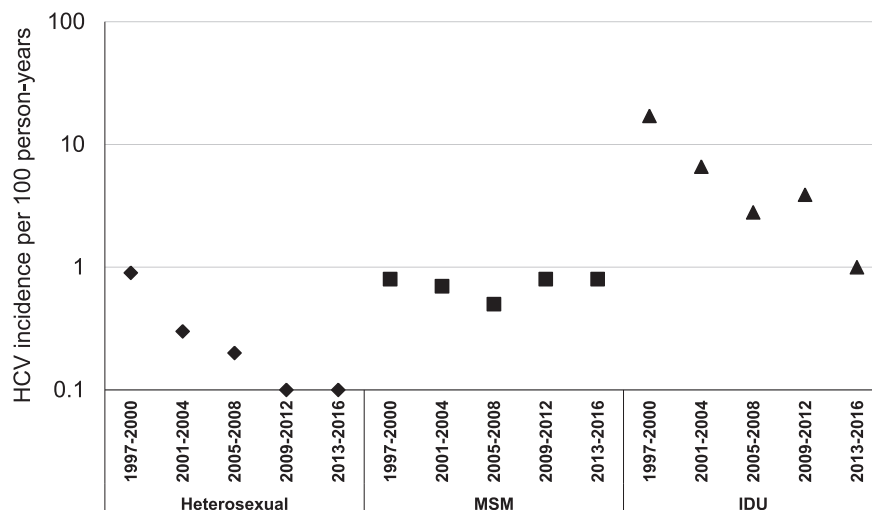
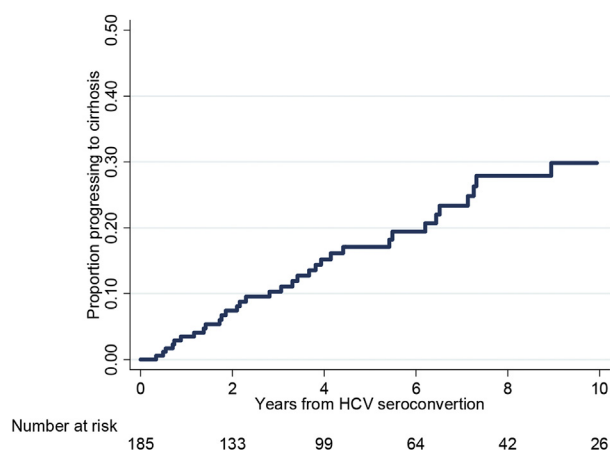


Figure 1. Incidence rates of hepatitis C virus seroconversion by calendar year and human immunodeficiency virus risk factor



**Figure 2.** Kaplan–Meier estimate of the probability of progressing to hepatitis C virus-related severe fibrosis/cirrhosis in persons living with human immunodeficiency virus with hepatitis C virus seroconversion in the Icona cohort

The advent of direct-acting antivirals has revolutionized the therapy of HCV infection, as 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 direct-acting antivirals treatment.

#### Transparency declaration

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#### Appendix A. Supporting information

Additional Supporting Information may be found in the online version of this article at <http://dx.doi.org/10.1016/j.cmi.2016.12.003>.

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