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ORIGINAL ARTICLE

Is HCV elimination among persons living with HIV feasible? Data from the NoCo study in the setting of the ICONA cohort

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Abstract

Background and Aims: Whether the HCV test-and-treat strategy impacted on the rate of new HCV infections among PLWH in Italy is unknown.

Methods: Prospective study of PLWH in the ICONA network. At baseline, PLWH were tested for HCV-Ab; HCV-RNA (if HCV-Ab positive) and, if positive, treated with DAA. SVR12 indicated eradication. Seroconversions and re-infections were evaluated yearly in HCV-Ab neg and HCV-RNA neg at first screening. We estimated the following: HCV seroconversions, incidence of HCV reinfections, and access to DAA and SVR12 rates tighter with factors associated with each outcome. Data were analysed by Cox regression, Poisson regression and logistic regression models.

Results: Sixteen thousand seven hundred and forty-three PLWH were included; 27.3% HCV-Ab positive; of these, 39.3% HCV-RNA positive. HCV seroconversion incidence: .48/100 PYFU (95% CI: .36–.65); re-infections incidence: 1.40/100 PYFU (95% CI: .91–2.04). The risk factor for HCV re-infection was young age: aIRR 1.85, 95% CI: 1.17–2.95) per 10 years younger. 86.4% of HCV viremic in follow-up started DAA. PWID vs. heterosexuals (aHR .75, 95% CI .62–.90), HIV-RNA >50 copies/mL

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(aHR .70, 95% CI .56–.87), HCV genotype other than G1, G2, G3, G4 or with multiple/missing HCV genotype and post-COVID-19 calendar periods were associated with lower DAA access. 922/965 (95.5%) PLWH achieved SVR12. We estimated 72% reduction of chance to achieve SVR12 in PLWH with a CD4 count <200/mm^3 (vs. CD4 ≥200/mm^3 aOR .18, 95% CI: .07–.46). 95.5% of DAA-treated individuals eradicated HCV, but they represent only 53.2% of HCV viremic PLWH and 66.4% of those in follow-up. HCV-RNA positivity by year decreased from 41.7% in 2017 to 11.7% in 2022. **Conclusions:** The screening-and-treat campaign implemented in Italy, even if only partially effective, resulted in a dramatic drop in HCV circulation in our cohort.

KEYWORDS
eradication, HCV, PLWH, reinfections, seroconversions

1 | INTRODUCTION

Hepatitis C virus (HCV) affects millions of individuals worldwide and results in severe hepatic damage ultimately leading to cirrhosis and cancer in most untreated individuals.[1–4] Direct antiviral agents (DAA) acting against HCV have been proven to be successful in determining HCV eradication from the body, thus avoiding liver damage and abating HCV transmission.[5–9] Consequently, in May 2016, the World Health Organization (WHO) adopted the first Global health sector strategy on viral hepatitis, 2016–2021, a strategy aiming at eliminating viral hepatitis as a public health treatment by 2030. The main goals of this strategy are the reduction of new viral hepatitis infections by 90% and the reduction of viral-hepatitis-related deaths by 65% by 2030.[10] The WHO strategy includes several agenda points towards HCV elimination, most importantly improving the cascade of care by scaling up diagnosis and treatment to prevent further transmissions. To reach this overarching goal, so-called micro-elimination interventions were proposed as a pragmatic approach, that is, focussing on specific target populations with high HCV prevalence and incidence.[11–13]

Historically, Italy has been considered the country with the highest rate of HCV prevalence and HCV-related mortality in Western Europe.[14] Following the availability of DAA in Italy, treatment has been extensively offered since 2015 to patients with a high risk of HCV-related complications and death and, since 2017, to all individuals known to be HCV viremic.[15]

One of the main obstacles to HCV elimination, in addition to new infections, is the high rate of re-infections observed in patients at risk, which could maintain HCV circulation.[16,17] Nevertheless, a free access to anti-HCV DAA, together with their high efficacy, has been demonstrated to curb this epidemic.[2] Recently, in many hepatitis elimination programs, COVID-19 has resulted to slow both re-infections and access to DAA. A 1-year delay in hepatitis diagnosis and treatment could have resulted in an additional 44 800 liver cancers and 72 300 deaths from HCV globally by 2030.[18]

HIV and HCV share the same way of transmission and indeed HCV circulates among persons living with HIV (PLWH). In Italy, among the PLWH enrolled in ICONA (Italian Cohort Naive Antiretrovirals), a cohort of HIV-positive individuals enrolled while naives from antiretrovirals, the prevalence of HCV at entry in the cohort is around 25%, ranging from 93% among people who inject drugs (PWID) to 7% among men-sex-with-men (MSM) and heterosexuals,[19] but active or former HCV infection, as well as re-infections, have never been fully monitored.

Key points

The HCV test-and-treat strategy to eliminate HCV among PLWH in Italy resulted in success in those on follow-up. In particular, there were few documented seroconversion and few reinfections as compared to other countries, but DAA uptake in participants with established chronic infection was instead low. By the end of the study, despite 95.5% SVR12 rate, only 53% of the whole study population eradicated the virus. The main obstacle was access to DAA, especially due to restrictions in care during the COVID-19 pandemic.

We describe a prospective observational study of PLWH seen for care at the Icona Network participating sites over the period 2017–2022, aimed at evaluating whether the introduction of recommendations for increased screening for HCV among PLWH after 2016, by International Guidelines,[10] together with the universal availability of DAA might result in HCV elimination among PLWH enrolled in the ICONA cohort, and to quantify the rate of new HCV infections and reinfections: the NoCo (No HCV Coinfection) study.

2 | METHODS

2.1 | Design of the study

Prospective observational study including PLWH seen for routine care at the Icona Network participating sites, aiming at evaluating whether recommendations of periodic HCV screening and treatment resulted in

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reducing/eliminating HCV replicative infections over the years 2017–2022 post-introduction of such recommendation (the NoCo study).

The ICONA network includes all the centres participating in the ICONA cohort, who collaborate in studies including also patients not belonging to the ICONA cohort.

2.2 | Objectives

- To estimate the prevalence of past and active HCV infection among PLWH in care in Italy over the period 2017–2022
- To estimate the incidence and predictors of HCV seroconversions and HCV re-infections
- To estimate the rate of DAA uptake and response to DAA among HCV viremic PLWH and associated factors

2.3 | Study population

The NoCo study includes PLWH screened for HCV infection from September 2017 to October 2022, seen for care at Infectious disease centres of the Italian ICONA network. Criteria to be included in the study were: belonging to a centre of the ICONA Foundation network, and having provided the informed consent to participate in the study. Baseline was the date of the first HCV screening test after September 1, 2017, date of study start.

In detail, the NoCo study was planned as follows. Icona Network participating sites have been encouraged to strictly follow the WHO recommendation regarding HCV testing and treat. These involved: (i) to test for HCV-Ab and, if antibody negative, the recommendation was to re-test them at least once a year, to ascertain the occurrence of seroconversions; (ii) for PLWH who resulted HCV-Ab positive, and those already known to be HCV-Ab positive, the recommendation was to test them for HCV-RNA, regardless of previous HCV treatment. In case of detectable HCV-RNA, to comply with the routine care practice of determining their HCV genotype and starting treatment with DAA; in case of undetectable HCV-RNA they should be scheduled to be re-tested yearly, to ascertain possible re-infections. Those treated with DAA were tested for HCV-RNA at end-of-treatment and 12 weeks thereafter. According to Guidelines,[10] they were considered cured when the 12-week post-DAA HCV-RNA was negative (sustained virologic response, SVR12) (Figure 1).

2.4 | Data collection

For all the patients enrolled, data collected included demographics (age, sex, risk factors of HIV/HCV acquisition, nation at birth (Italy

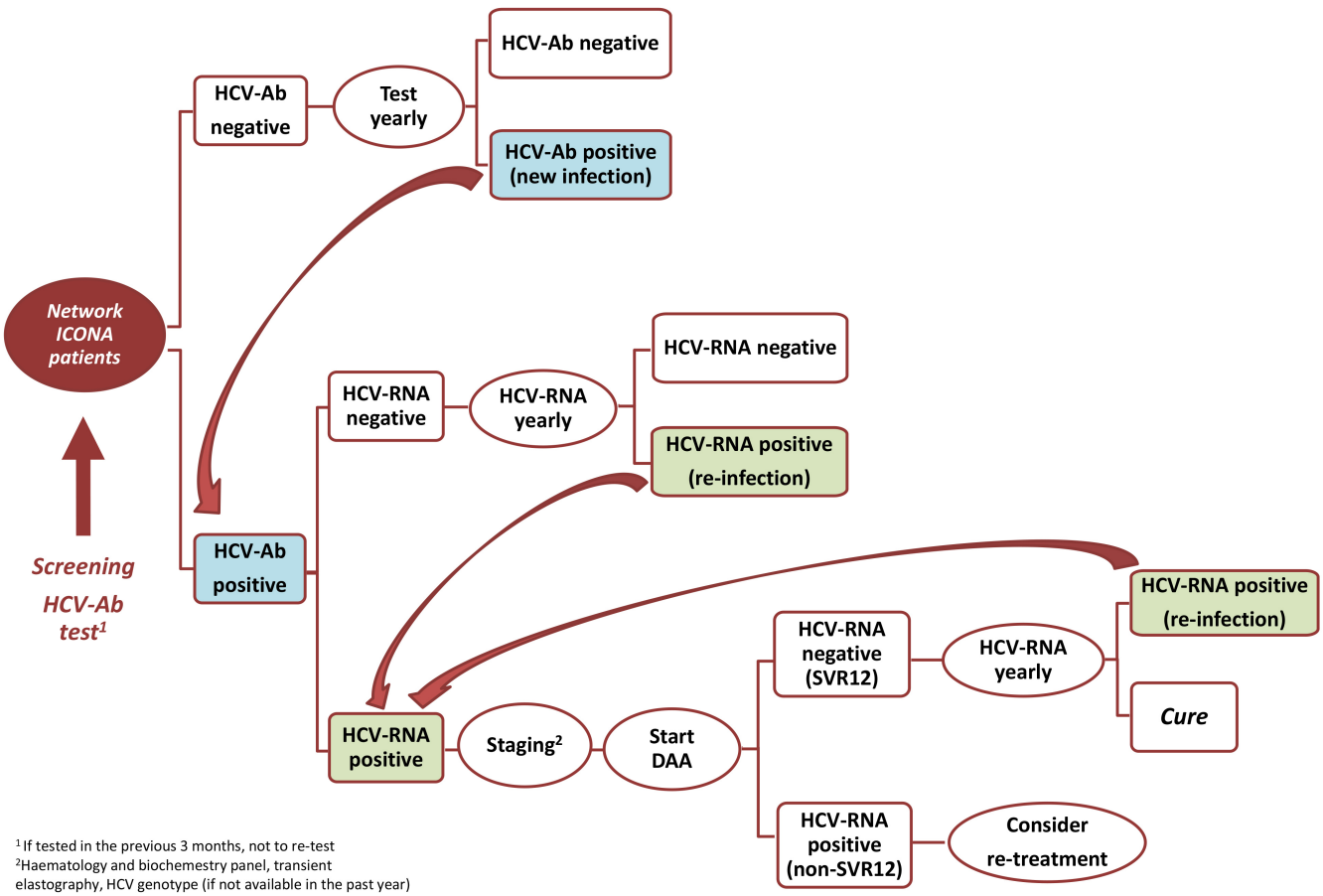

FIGURE 1 Test-and-treat recommendations according to 2016 WHO Guidelines.

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vs. other)), HIV-related data (date of HIV diagnosis, CD4 cell count, HIV-RNA, date of first antiretroviral therapy initiation), other hepatitis data (HBsAg) and HCV related data (date of first diagnosis, previous use of interferon and/or corticosteroids, or DAA; HCV-RNA, HCV genotype, liver cirrhosis at baseline, FIB-4 score,[20] as well as the yearly screening data of HCV-Ab or HCV-RNA.

The data were frozen on October 31, 2022.

The NoCo study was approved by all the Ethic Committees of participating centres. All PLWH signed an informed consent for study participation and processing of data.

2.5 | Statistical analyses

2.5.1 | Prevalence of HCV infection at baseline

Time zero for the analyses (baseline) was the first date of HCV-Ab and/or HCV-RNA test after enrollment in the NoCo study, in the time-frame 2017–2022.

The prevalence of HCV infection (HCV-Ab positivity) and active HCV infection (HCV-RNA positivity among HCV-Ab positives) was evaluated at baseline. We compared the demographic and clinical characteristics of PLWH with and without HCV infection (HCV-Ab). In a second analysis, we compared demographic and clinical characteristics of PLWH with evidence of a past HCV infection which was cleared (HCV-Ab positive, HCV-RNA negative), with those with active, replicating HCV infection (HCV-RNA positive). We also calculated the prevalence of HCV-RNA positivity according to calendar year. Chi-square test and Wilcoxon Rank Sum tests were used to compare the groups, as appropriate.

2.5.2 | Prevalence and incidence of HCV seroconversions and re-infections

The prevalence and incidence of HCV seroconversions, in HCV-Ab negatives at baseline, were calculated as well as the cumulative probability of HCV seroconversions by Kaplan Meier curves at 1, 2 and 4 years from enrolment Only HCV-Ab negative PLWH with at least a subsequent HCV-Ab screening have been included in these calculations. Predictors of HCV seroconversion were identified by unadjusted and adjusted Cox regression models, exposures of interest in the model were sex, mode of HIV transmission, age, nation of birth (Italian vs. non-Italian), calendar period of first NoCo screening (COVID-19 vs. pre-COVID-19, using the threshold of 2020) and years from HIV diagnosis. For all the HCV-Ab positive/HCV-RNA negative PLWH at first NoCo screening, with at least one following HCV-RNA measurement, the incidence of HCV re-infections (HCV-RNA turned to positive), was evaluated and predictors were identified by means of Poisson regression analysis; covariates of interest for the identifications of predictors were sex, mode of HIV transmission, age and calendar period of NoCo enrolment. A Poisson model and relative rates of developing the outcome associated with covariates (instead of a Cox regression model like for the other outcomes) were conducted here for consistency with the univariable analysis which produced incidence rates per 100 person years of follow-up (PYFU).

2.5.3 | Probability of DAA uptake and of SVR12

Standard survival methods (Kaplan–Meier curves) were used to estimate the probability of DAA-uptake in HCV-RNA positive participants who also had at least one follow-up visit. Follow-up time accrued from the date of the first HCV-RNA positive test result. Unadjusted and Adjusted Cox models were used to identify the predictors of DAA-start. The following factors were investigated as potential predictors of DAA-initiation: sex, mode of HIV transmission, age, calendar period (COVID-19 vs. pre-COVID-19 screening date), HCV-genotype, baseline HIV-RNA, CD4 and FIB-4 strata. In all survival analyses, potential confounders, and adjustment sets, for each of the exposure of interest were identified according to the assumptions shown in the directed acyclic graph (DAG) in Figure S1A.

Percentage of DAA-treated PLWH reaching SVR12 was calculated. Because of the short time of follow-up, we modelled SVR12 as a binary outcome and logistic regression models were used to investigate predictors of SVR12. The following factors were investigated as potential predictors of DAA initiation: mode of HIV transmission, HCV-genotype, DAA regimen started, baseline HIV-RNA, CD4 and FIB-4 strata (Figure S1B).

2.5.4 | Calendar year prevalence of active-HCV PLWH

We finally examined the prevalence of active HCV infection PLWH in the time-frame of the study according to calendar year of follow-up. We included all the HCV-Ab positive PLWH tested for HCV-RNA each year; Chocran-Armitage test was used to analyse the trend by years.

3 | RESULTS

A total of 16 743 PLWH recruited from 51 Infectious Diseases centres belonging to the ICONA Foundation Network were included in the study. Pre-screening HCV data, resulted in 9363 (55.9%) HCV-Ab negative, 4331 (25.9%) HCV-Ab positive and 3049 (18.2%) with unknown HCV serology. At first screening (baseline), 12 174 (72.7%) resulted to be HCV-Ab negative and 4569 (27.3%) HCV-Ab positive. Demographic and clinical characteristics according to HCV status at baseline are shown in Table 1. HCV-Ab positive individuals were older, more frequently females and born in Italy, with a longer duration of HIV diagnosis; median CD4 counts/cmm were higher and HIV-RNA copies/mL lower in HCV coinfected PLWH.

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TABLE 1 Characteristics of 16 743 PLWH at first NoCo screening according to HCV-Ab status at first screening.

	Anti-HCV neg	Anti-HCV pos		Total
	N = 12 174 (72.7%)	*N* = 4569 (27.3%)	*p*-value	*N* = 16 743 (100.0%)
Age, years, median (IQR)	46 (37–54)	54 (49–57)	<.001	49 (40–56)
≥50 years	4817 (39.6)	3364 (73.6)		8181 (48.9)
Sex, male, *n* (%)	9613 (79.0)	3451 (75.5)	<.001	13 064 (78.0)
Nationality, Italian, *n* (%)	9543 (78.4)	4298 (94.1)	<.001	13 841 (82.7)
Mode of HIV transmission, *n* (%)			<.001	
Heterosexual	5095 (41.8)	599 (13.1)		5694 (34.0)
PWID	347 (2.9)	3163 (69.2)		3510 (21.0)
MSM	5237 (43.0)	555 (12.1)		5792 (34.6)
Other/Unknown	1495 (12.3)	252 (5.5)		1747 (10.4)
On ART, *n* (%)	9234 (75.8)	3957 (86.6)	<.001	13 191 (78.8)
Years from HIV diagnosis	5.9 (1.2–12.2)	22.6 (12.8–30.4)	<.001	8.5 (2.5–19.2)
CD4, cells/mmc, median (IQR)	598 (366–832)	644 (426–895)	<.001	610 (384–850)
HIV-RNA < 50 copies/mL, *n* (%)	5063 (66.0)	2690 (87.6)	<.001	7753 (72.1)
Year 1st NoCo screening			<.001	
2017	153 (1.3)	107 (2.3)		260 (1.5)
2018	4744 (39.0)	2701 (59.1)		7445 (44.5)
2019	4752 (39.0)	1307 (28.6)		6059 (36.2)
2020	1123 (9.2)	228 (5.0)		1351 (8.1)
2021	1014 (8.3)	172 (3.8)		1186 (7.1)
2022	388 (3.2)	54 (1.2)		442 (2.6)

A total of 4411/4569 (96.5%) HCV-Ab positive were tested for HCV-RNA; of these, 1732 (39.3%) were HCV-RNA positive at baseline. HCV viremic individuals were younger, less frequently born in Italy, less frequently PWID, with a more recent HIV diagnosis, and a more severe liver disease as documented by FIB-4 index (Table 2).

For the prospective analysis, we examined only 7560 (45.1%) PLWH with at least one follow-up visit after baseline. Of the 1732 HCV-RNA positive, 345 (19.9%) had no follow-up visit. These PLWH were more frequently non-Italians, less frequently ART treated, with lower CD4 counts, and more frequently with baseline screening in the Covid-19 period (see Table S1).

3.1 | HCV seroconversions

Over a median follow-up of 1.64 (IQR: 1.00–2.43) years, we observed 42 HCV-Ab seroconversions in 4890 HCV-Ab negative PLWH who underwent at least a second screening, giving an incidence of .48/100 person-years follow-up (PYFU) (95% CI: .36–.65). The highest incidence rate (IR) was observed among MSM (.60/100 PYFU – 95% CI: .41–.87), and the lowest in heterosexuals (.37/100 PYFU – 95% CI: .21–.65), with intermediate IR of HCV among PWID (.39/100 PYFU – 95% CI: .05–2.8). The Kaplan–Meier cumulative probability of HCV seroconversion was .5% (95% CI: .3–.7) at 1 year, 1.0% (95% CI: .7–1.5) at 2 years and 1.6% (95% CI 1.1–2.4) at 4 years (Figure S2). By Cox regression analysis, none of the factors analysed (age, sex, mode of HIV transmission, nation of birth, years from HIV diagnosis) was independently associated with a higher risk of HCV seroconversion (Table S2).

3.2 | HCV re-infections

Over a median follow-up of 1.3 (95% CI: .7–2.4) years, 35 out of 1144 (3.0%) PLWH with cleared HCV infection (HCV-Ab positive/HCV-RNA negative at baseline), turned to HCV-RNA positive (one subject had 2 HCV re-infections in the study period). Of these, 10 turned to HCV-RNA positive less than 12 weeks after DAA completion and were considered relapses; the remaining 25 were confirmed cases of HCV re-infections during the study (9 of them had been previously successfully treated with DAA and 9 with Peg-IFN/RBV). The incidence of HCV re-infections was 1.40/100 PYFU (95% CI: .91–2.04). Again, the highest IR was observed among MSM (2.24/100 PYFU – 95% CI: .82–4.89) and the lowest among heterosexuals (1.01/100 PYFU – 95% CI: .12–3.64). However, by multivariate Poisson model, there were no differences according to mode of transmission of HIV; sex or calendar period of first screening (COVID-19 vs. pre-COVID-19 screening period); younger individuals showed a higher incidence of HCV re-infection, with 87% increase (aIRR 1.87, 95% CI: 1.17–2.97) per 10-year younger age (Table 3). We found a difference in the risk of

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TABLE 2 Characteristics of HCV-Ab pos PLWH according to HCV–RNA at first screening.

	HCV-RNA neg	HCV–RNA pos		Total
	N = 2679 (60.7%)	*N* = 1732 (39.3%)	*p*-value	*N* = 4411 (100.0%)
Age, years, median (IQR)	54 (50–58)	53 (47–56)	<.001	54 (49–57)
<30	29 (1.08)	25 (1.44)		54 (1.22)
30–39	110 (4.11)	137 (7.91)		247 (5.6)
40–49	429 (16.01)	395 (22.81)		824 (18.68)
50–59	1680 (62.71)	981 (56.64)		2661 (60.33)
≥60	431 (16.09)	194 (11.2)		625 (14.17)
Sex, male, *n* (%)	2050 (76.5)	1285 (74.2)	.079	3335 (75.6)
Nationality, Italian, *n* (%)	2565 (95.7)	1599 (92.3)	<.001	4289 (94.0)
Mode of HIV transmission, *n* (%)			.001	
Heterosexual	343 (12.8)	207 (11.9)		550 (12.5)
PWID	1913 (71.4)	1188 (68.6)		3101 (70.3)
MSM	273 (10.2)	246 (14.2)		519 (11.8)
Other/Unknown	150 (5.6)	91 (5.2)		241 (5.5)
On ART, *n* (%)	2269 (84.7)	1586 (91.6)		3957 (86.6)
CD4 count, cells/mmc, median (IQR)	685 (448–931)	611 (408–847)	<.001	648 (430–897)
<200 CD4 cells/mmc, *n* (%)	92 (5.9)	97 (7.0)	.255	189 (6.4)
HIV-RNA, cps/mL, median (IQR)	1 (1–29)	19 (1–35)	<.001	1 (1–29)
<50 cps/mL, *n* (%)	1402 (90.4)	1215 (87.1)	.004	2617 (88.9)
Years from HIV diagnosis	24.5 (15.3–30.9)	21.0 (11.4–19.5)	<.001	23.0 (13.4–30.5)
Year 1st NoCo screening			<.001	
2017	50 (1.9)	57 (3.3)		107 (2.4)
2018	1518 (56.7)	1141 (65.9)		2659 (60.3)
2019	868 (32.4)	377 (21.8)		1245 (28.2)
2020	137 (5.1)	77 (4.4)		214 (4.8)
2021	81 (3.0)	20 (1.1)		141 (3.2)
2022	25 (.9)	20 (1.1)		45 (1.0)
FIB-4	1.38 (.99–1.99)	1.55 (1.08–2.26)	<.001	1.47 (1.04–2.11)
<1.45	817 (30.5)	586 (33.8)		1403 (31.8)
1.45–3.25	591 (22.1)	579 (33.4)		1170 (26.5)
>3.25	129 (4.8)	171 (9.9)		300 (6.8)
Missing	1142 (42.6)	396 (22.9)		1538 (34.9)
Previous anti-HCV treatment			<.001	
No	262 (9.8)	1105 (41.3)		1367 (51.0)
Peg-IFN + RBV	560 (20.9)	219 (8.2)		779 (29.1)
DAA	761 (28.4)	120 (4.5)		881 (32.9)
Missing	1095 (40.9)	288 (10.8)		1383 (51.6)
HCV-genotype				
Gen.1		744 (43.0)		
Gen.2		50 (2.9)		
Gen.3		308 (17.8)		
Gen.4		131 (13.3)		
Other/Multiple or missing Gen.		399 (23.0)		

re-infections for younger individuals according to mode of transmission (*p* value for interaction: .035): actually, only among PWID younger individuals were at higher risk of re-infection, whereas this was not the case of MSM: PWID per 10-years younger aIRR 2.73 (95% CI: 1.60–4.66); MSM per 10 years younger: aIRR 1.05 (95% CI: .48–2.29).

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3.3 | DAA uptake and predictors

A total of 1199 out of 1387 (86.4%) HCV viremic PLWH with at least one follow-up visit started DAA. The Kaplan Meier cumulative probability of DAA uptake was of 79.2% (IQR:76.9–81.4) at 1 year and 91.5% (IQR: 89.2–92.7) at 2 years. A total of 670 (55.9%) started a DAA regimen with sofosbuvir/velpatasvir and 409 (34.1%) with the combination glecaprevir/pibrentasvir; other DAA regimens (elbasvir/grazoprevir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/r/+dasabuvir±ribavirin, sofosbuvir/velpatasvir/voxilaprevir) counted for 10.0% ($n=120$).

The predictors of access to DAA by univariable and multivariable analyses are shown in Table 4. By univariable analysis, PWID showed lower chance to access DAA as compared to heterosexuals; longer time from HIV diagnosis, current HIV-RNA >50 copies/mL, CD4 counts <200/cmm and COVID-19 pandemic screening years (2020–22) vs. previous years (2017–19) were also associated with

TABLE 3 Factors associated with HCV re-infection for 1144 PLWH with past HCV infection, Poisson regression model.

	IRR	95% CI		p	aIRR[a]	95% CI		p
Sex M (vs. F)	2.17	.65	7.20	.206	2.38	.67	8.43	.18
Mode of HIV transmission								
Heterosexual	1.00				1.00			
PWID	1.26	.29	5.47	.755	1.16	.26	5.17	.845
MSM	2.66	.54	13.21	.157	1.16	.21	6.47	.867
Other/Unknown	1.81	.25	12.84	.554	1.79	.25	12.78	.564
Calendar period, COVID (≥2020) vs. pre-COVID (<2020)	1.17	.16	8.65	.875	1.26	.17	9.40	.822
Age, per 10 years younger	1.82	1.21	2.71	.004	1.87	1.17	2.97	.008

[a]Adjusted for all the factors shown in table.

TABLE 4 Predictors of access to DAA by univariable and multivariable Cox analysis among 1184 HCV viremic PLWH.

	HR	95% CI		p	aHR[a]	95% CI		p
Sex M (vs. F)	.99	.87	1.12	.971				
Mode of HIV transmission								
Heterosexual	1.00				1.00			
PWID	.94	.78	1.12	.479	.75	.62	.90	.002
MSM	1.00	.81	1.25	.967	1.02	.82	1.27	.853
Other/Unknown	1.37	1.03	1.81	.031	1.18	.89	1.57	.248
Age, per 10 years increase	1.13	1.05	1.21	.001	1.03	.95	1.12	.522
Italian (vs. Non-Italians)	.88	.69	1.12	.301				
Year HIV infection, per 1 year more	1.16	1.10	1.22	<.001				
Calendar year, COVID (≥2020) vs. pre-COVID (<2020)	.71	.57	.89	.003	.73	.58	.91	.005
HIV-RNA >50 copies/mL	.60	.48	.75	<.001	.70	.56	.87	.002
CD4 <200 cells/mmc	.55	.41	.75	<.001	.79	.62	1.01	.062
FIB-4								
FIB-4 >3.25	1.00				1.00			
FIB-4 1.45–3.25	1.28	1.05	1.57	.014	1.19	.98	1.46	.086
FIB-4 <1.45	1.11	.91	1.36	.294	1.10	.90	1.35	.355
FIB-4 missing	.78	.60	1.01	.06	.88	.67	1.14	.327
HCV genotype								
G1 or G4	1.00				1.00			
G2 or G3	.94	.82	1.08	.367	.93	.82	1.07	.324
Other/Multiple/Missing	.51	.42	.64	<.001	.59	.48	.74	<.001

[a]Set of adjustment for each factor:- CD4: adjusted for sex, year of HIV infection, HIV-RNA; FIB-4: adjusted for mode of HIV transmission, year of HIV infection; HCV-Genotype: adjusted for mode of HIV transmission; HIV-RNA: adjusted for Italian, mode of HIV transmission; Mode of HIV transmission: adjusted for year of HIV infection; Age: adjusted for mode of HIV transmission, year of HIV infection; calendar period: adjusted for age and Italian.

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a lower probability of starting DAA. Older PLWH and those with FIB-4 >3.25 had higher probability to initiate DAA. After controlling for confounders, PWID vs. heterosexuals (aHR .75, 95% CI .62–.90), a current HIV-RNA >50 copies/mL (aHR .70, 95% CI .56–.87) and being infected by HCV genotype other than G1, G2, G3, G4 or multiple genotypes or with missing information (aHR = .59, 95% CI .48–.75) all remain statistically significant associations. CD4 counts <200/cmm at baseline were associated with a non-statistically significant lower probability to access to DAA (aHR .79, 95% CI .62–1.01 vs. CD4 >200/cmm). The calendar period of the first NoCo screening has been found to be associated with DAA start, with a significant lower risk of start during COVID-19 pandemic period (2020–2022 vs. 2017–2019 aHR = .73, 95% CI .58–.91).

3.4 | Outcome and predictors of DAA

A total of 965/1199 (80.5%) PLWH reached 12 weeks of follow-up after their DAA full cycle; of these, 922 (95.5%) achieved a negative HCV-RNA test result by 12 weeks, documenting cure (Sustained virological response, SVR12). We ran several regression analyses focussed on evaluating the independent role of individual variables possibly related with achieving SVR12, after adjusting for slightly different sets of confounders in each analysis. The only independent predictor of SVR12 was CD4 counts: PLWH with CD4 counts ≤200/cmm had a 72% reduction in the chance of acheiving SVR12 (vs. CD4 >200/cmm aOR = .18, 95% CI: .07–.46) (Table 5).

3.5 | HCV picture by the end of NoCo study

In summary, we observed that all the enrolled patients with missing HCV-Ab (3049/16743; 18.1%) were eventually tested, according to the recommendations criteria of the NoCo study and that 6.3% of these were indeed HCV-Ab-positive participants who have been potentially missed; the vast majority (4411/4569–96.5%) of HCV-Ab positive were tested for HCV-RNA; of these, 1732 (39.3%) resulted to be HCV viremic. Most of these (n = 1387, 80.1%) have been follow-up over time.

TABLE 5 Predictors of non-SVR12 among 965 PLWH initiating DAA by fitting logistic regression analysis.

	OR	95% CI		p	aOR[a]	95% CI		p
Sex	.90	.44	1.86	.778				
Mode of HIV transmission								
Heterosexual					1.00			
PWID	.89	.34	2.35	.820	.68	.25	1.90	.465
MSM	7.20	.83	62.50	.073	7.66	.88	66.62	.065
Other/Unknown	.40	.12	1.36	.142	.34	.10	1.17	.087
Age, per 10 years increase	1.00	.67	1.48	.983				
Non-Italian (vs. Italian)	.39	.15	1.04	.059				
Year HIV infection, per 1 year more	1.06	.78	1.43	.710				
HIV-RNA >50 copies/mL	.94	.28	3.14	.923	.97	.28	3.34	.964
CD4 <200 cells/mmc	.15	.06	.36	<.001	.18	.07	.46	<.001
FIB-4								
FIB-4 >3.25	1.00				1.00			
FIB-4 1.45–3.25	2.71	1.21	6.08	.016	1.97	.83	4.70	.124
FIB-4 <1.45	3.75	1.59	8.85	.003	2.21	.84	5.78	.106
FIB-4 missing	2.44	.51	11.66	.264	1.48	.29	7.59	.636
HCV genotype								
G1 or G4	1.00				1.00			
G2 or G3	1.08	.52	2.23	.845	1.15	.55	2.39	.717
Other/Multiple/Missing	.77	.18	3.38	.734	.97	.21	4.44	.972
DAA Regimen								
GCV/PBV	1.00				1.00			
SOF/VEL	.72	.36	1.45	.356	.83	.41	1.68	.598
Other regimen	.44	.14	1.41	.166	.48	.14	1.60	.231
Missing	.46	.06	3.84	.477	.44	.05	3.77	.452

[a]Set of adjustments for each factor: FIB-4: adjusted for HIV-RNA, CD4, HCV genotype, mode of HIV transmission; HCV-Genotype: adjusted for mode of HIV transmission, year hiv infection; DAA regimen: adjusted for HIV-RNA, FIB-4, HCV genotype, mode of HIV transmission; CD4: adjusted for HIV-RNA, FIB-4, HCV genotype, mode of HIV transmission; HIV-RNA: adjusted for CD4, FIB-4, HCV genotype, mode of HIV transmission; Mode of HIV Transmission: adjusted for year hiv infection.

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Thus, as already described, even if 95.5% of the DAA-treated viremic individuals eradicated HCV, this percentage represents only 53.2% (922/1732) of the total burden of HCV viremic PLWH in ICONA, and 66.4% (922/1367) of those in follow-up.

These data were confirmed also after excluding non-Italian PLWH (data not shown).

3.6 | Yearly prevalence of active HCV infection at cohort level

The prevalence of HCV-RNA positivity was decreasing per more recent calendar year from 41.7% (48/115) in 2017; to 23.8% (676 /2838) in 2018; 16.4% (437 /2658) in 2019; 14.4% (165/1143) in 2020; 12.1% (98/809) in 2021; 11.7% (40/342) in 2022 (Cochran-Armitage test: $p < .001$). (Figure S3).

4 | DISCUSSION

Our study aimed at evaluating the extent of decreased circulation of HCV among PLWH belonging to the ICONA network, thanks to the availability of HCV eradicating antivirals and following the recommendations of extensive HCV screening by International Guidelines. The changes in routine clinical practice of PLWH appeared to be successful in our Network although the lack of complete follow-up for some participants does not allow us to fully evaluate their impact. Indeed, DAA was successful in eradicating HCV in more than 95% of fully treated PLWH, and re-infections were rare in our setting. Nevertheless, DAA uptake was limited to 69.2% of HCV viremic, resulting in only 66.4% of PLWH in follow-up fully cured, and in 53.2% cured in the whole HCV-infected cohort.

In more detail, increased rate of screening resulted in the identification of HCV status in 18% of the enrolled PLWH who were never been tested for HCV-Ab. It is quite surprising that in a setting of HI0V clinics, still 18% of PLWH were not tested for HCV, as European HIV Guidelines recommended to screen annually for hepatitis markers even before the 2016 WHO guidelines[10,21]; nevertheless, it has to be taken into account that about half of the study occurred during the worse period of the SARS CoV-2 epidemic, in 2020–21, and at that time Infectious Disease doctors were fully engaged in COVID-19 care, leaving all the other commitments at basic levels.

At study baseline, more than a quarter of PLWH had a previous or ongoing HCV infection, and, as expected, PWID were the group more frequently HCV coinfected, as the two viruses share the same way of transmission.[22] HCV epidemic among PWID started even before that of HIV,[23] thus it is not surprising that older individuals, born in Italy, showed the highest prevalence of HCV co-infection; they have also typically been diagnosed with HIV earlier and showed a better viro-immunologic asset. The higher HCV prevalence among females was observed in previous analyses of the data of the ICONA cohort.[24]

The incidence of seroconversion in our cohort was low, consistently with the data observed in ICONA cohort several years ago: overall, in 1997–2016, the incidence rate (IR) of seroconversions was .6/100 PYFU and in 2017–2023 the IR was of .48/100 PYFU.[25] Only among PWID, there was a sharp reduction of seroconversion incidence, ranging from 1/100 PYFU in 2013–2016 to .39/100 PYFU in 2017–2022.[25] We also confirmed that at present MSM was the group with the highest incidence of new HCV infection although with a rate which is much lower that than seen in MSM in North Europe.[26] Possible explanations include lower frequency of promiscuous sexual practices, including chem sex abuse, associated with more risky sexual behaviours[27] in MSM from Southern vs. Northern Europe and the availability of universal anti-HCV treatment during the study period.

Re-infections were more frequent than seroconversions, and, after excluding the relapses, the incidence of cases turning from HCV-RNA negative to positive was 1.40/100 PYFU. Again, this incidence is lower than reported by other authors.[28] Interestingly, the only predictor of the risk of re-infection was age, with a risk which increases by 85% per 10-year younger age. It is well known that risky behaviours are less frequent with older age. Of note, Hosseini-Hooshyar and colleagues[29] reported the results of a meta-analysis on 41 studies highlighting that re-infection occurs more frequently in MSM; we failed to detect such association, possibly because of low statistical power.

What is most intriguing, is the relatively low percentage of DAA initiation among HCV viremic individuals in our study. Indeed, against the expectation that almost all PLWH with indication for treatment had been treated by now, only 86% (1199 out of 1372) of those in follow-up appeared to have initiated DAA. Factors associated with a reduced probability of starting DAA, (i.e. being PWID, and harbouring multiple genotypes, indicative of persistent risky behaviour) in our analysis are all known barriers to DAA uptake.

Other groups of participants who were identified as having a lower chance of accessing DAA treatment were those with more advanced HIV infection, documented by detectable HIV-RNA (likely to be caused either by low adherence or a recent late HIV diagnosis) and low CD4 counts (marginally significant). It is possible that, in these more fragile subsets of the population, clinicians decided to wait for DAA initiation until HIV infection had been better controlled. This might have been particularly true during the years of COVID-19 epidemics, as perhaps demonstrated by our data. During the pandemic period, not only PLWH, especially the elderly, were frightened of going to hospital, but also doctors, who had to assist a multitude of COVID-19 patients, had to pause the liver outpatients clinics.

The rate of response to DAA was impressive in our study with >95% of DAA-treated PLWH who reached the 12 weeks after end-of-treatment that resulted to be cured, and aviremic. Furthermore, when we investigated possible predictors of HCV cure we identified only severe immunodepression to be associated with lower probability of eradicating HCV, after controlling for measured confounding. These results are consistent with those of many others showing that response to DAA in PLWH is reduced in case of severe

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immunodepression, while it is similar to the HIV uninfected patients in case of controlled immune-virological status.[30] Further, at a time in which there was no effective therapy against HCV, we had already shown that individuals with low CD4 counts were at higher risk of progression of HCV-related liver disease.[24,25]

Our study has several limitations: first of all the large percentage of participants who were lost to follow-up may have resulted in over-estimation of DAA success and HCV elimination rate. The reason for missing visits is unknown but is likely to be associated with poor prognosis. However, over the 2 years of the pandemic missing data might have been more random and linked to both disruption of the services and lack or delay in data recording. Nevertheless, at population level, the prevalence of HCV viremic individuals among HCV-Ab positive PLWH of the cohort, dramatically dropped from 42% in 2017 to 6% in 2021 which is undoubtedly a great success.

Second, because of the observational nature of the study, the detected associations are only robust under the usual assumptions of no unmeasured confounding and correct specified models.

In conclusion, the test and treat campaign which was promoted by WHO and implemented in Italy in recent years resulted in an important drop in HCV circulation in our cohort. Our data emphasize the need to maintain high rates of HCV monitoring and DAA treatment in order to definitively abate this life-threatening disease also in PLWH. In particular, information campaigns on the risk of acquiring HCV and chance of HCV eradication should be specifically addressed to fragile populations such as migrants and PWID.

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DATA AVAILABILITY STATEMENT

The database of the study is available only upon written and motivated request to the corresponding author.

ETHICS STATEMENT

The study has been approved by Ethic Committees of all the participating centers, all the patients signed informed consent before enrollment.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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