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# Unawareness of HCV serostatus among persons newly diagnosed with HIV

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ABSTRACT

Treatment of chronic HCV infection with direct acting antivirals can achieve high rates of sustained viral response in persons with HIV. In the perspective of HCV elimination in this population, high rates of HCV detection will be needed. We evaluated the unawareness of HCV infection in 2927 persons newly diagnosed with HIV during 2004–2015 in Rome, Italy. Two-hundred-fifty persons (8.5%) were anti-HCV positive. The proportion of HCV-unaware individuals at the time of HIV diagnosis was 58.0% (145/250), without significant variations over time, 17.2% showed an advanced fibrosis stage. The absence of previous HIV testing was significantly associated with HCV unawareness.



## Introduction

Chronic hepatitis C virus (HCV) infection has emerged in the past two decades as a major cause of morbidity and mortality among persons living with the human immunodeficiency virus (HIV) (PLWH) in high-income countries [1]. HIV and HCV have overlapping modes of transmission, and in 2015 it has been estimated that 6.2% of the 36.9 million people living with HIV worldwide (i.e. approximately 2.3 million people) were coinfected with HCV [2]. Prevalence of HCV infection among persons with HIV varies in different population groups, being highest among in men who have sex with men (6.4%), and in injecting drug users (82.4%) [2].

Recently, it has been shown that treatment regimens including new direct acting antivirals (DAAs) can achieve high rates of sustained viral response also in HCV-HIV coinfected persons [3]. Modeling studies and preliminary observational data show that a widespread use of DAAs may determine a reduction in HCV prevalence and prevent onwards transmission among PLWH [4,5]. Nonetheless, high rates of HCV detection and treatment will be needed to achieve these goals [5,6].

It is generally estimated that a high proportion of persons living with HCV is undiagnosed [7], although little information is available on undiagnosed HIV-HCV coinfection. We aimed to estimate temporal trends of prevalence and determinants of undiagnosed HCV infection among persons newly diagnosed with HIV.

## Material and methods

We analyzed data on persons newly diagnosed with HIV at "Lazzaro Spallanzani" Institute for Infectious Diseases in Rome, Italy, during 2004–2015, enrolled in a prospective observational study (SENDIH) [8]. For person enrolled in this study, demographic, epidemiological, laboratory and clinical data and information on previously diagnosed infections, including HCV, are prospectively collected through a standardized interview. HCV serology is routinely offered to all HIV-positive individuals, and if anti-HCV positive, HCV RNA is performed. The study was approved by the

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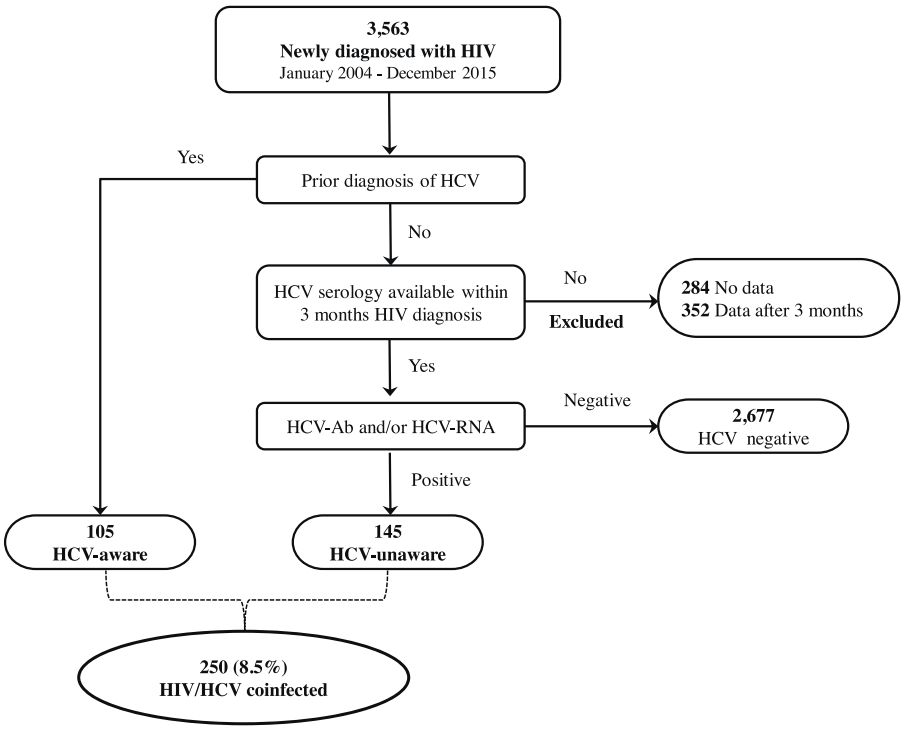



**Fig. 1.** Flow chart of the study.

Institute's Ethic committee, and enrolled individuals provide written informed consent.

We included in the analysis persons for whom HCV serology was available within 3 months HIV diagnosis and those for whom anamnestic anti-HCV positivity was available. We defined HCV-unaware, anti-HCV positive individuals who did not report a diagnosis of hepatitis C or a positive HCV test before HIV diagnosis. Staging of liver disease among anti-HCV positive individuals was obtained by the Fibrosis 4 (FIB-4) score, calculated as: age (years) × AST (U/L)/platelets ($10^9$/L) × ALT (U/L)$^{1/2}$. A FIB-4 score higher than or equal to 3.25 was used to define advanced liver disease [9]. Late HIV diagnosis was defined as a CD4 count <350 cells/mmc or an AIDS-defining event within 3 months of HIV diagnosis [10].

To identify factors associated with being HCV-unaware, univariable and multivariable logistic model were used, odds ratios, 95% confidence intervals and p-values were reported. We included in the multivariable model factors associated with unawareness of HCV infection in univariable analysis with a p-value less than 0.1. Values of $p < 0.05$ were considered statistically significant. All statistical analyses were conducted using StataCorp 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

## Results

From January 2004 to December 2015, 3563 individuals were newly diagnosed with HIV: 636 (17.8%) lacking anamnestic and/or serologic information on HCV infection within 3 months of HIV diagnosis were excluded from the analysis. Of the 2927 HIV positive persons included in the analysis, 250 resulted anti-HCV positive with an overall prevalence rate of 8.5% (Fig. 1). The rate of anti-HCV positivity decreased significantly over time being 15.3% in 2004–2006, 8.8% in 2007–2009, 7.4% in 2010–2012 and 4.5% in 2013–2015 ($p < 0.001$ by chi-square for trend). No significant trends over time in anti-HCV prevalence were observed stratifying by mode of infection (Fig. 2).

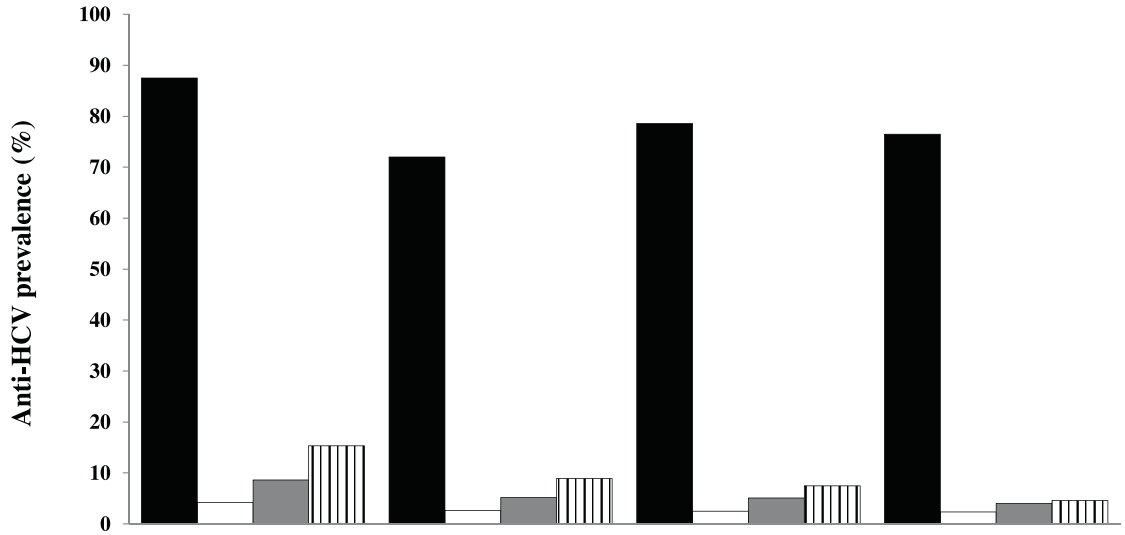
HCV RNA testing within 3 months of HIV diagnosis was available for 181 HCV-positive individuals, and 143 (79.0%) were viremic. Among the anti-HCV positive persons, 40 (16.0%) had a FIB-4 score ≥ 3.25 indicative of advanced liver fibrosis, while for 17 (6.8%) laboratory data to calculate the score were not available within three months from diagnosis. Among the persons with a FIB-4 score, 22 (9.4%) had a platelet count below $100 \times 10^9$/L.

Among 105 persons who reported a previous diagnosis of HCV infection, the median time from HCV to HIV diagnosis was 9.6 years (Interquartile range [IQR]: 4.1–14.5). Sixteen (15.2%) of them did not report any HIV-negative test and, they eventually resulted HIV-positive a median of 8.4 years (IQR: 3.1–14.8) from HCV positivity.

Overall, 145 anti-HCV positive persons (58.0%) were unaware of their serostatus at the time of HIV diagnosis. A FIB-4 score ≥ 3.25 was recorded for 25 (17.2%) HCV-unaware individuals and, among the 104 HCV-unaware individuals for whom HCV RNA was available, 85 (81.7%) tested positive.

The proportion of HCV-unaware individuals did not show significant variations over time (Table 1).

At univariable analysis, the probability of being HCV-unaware was higher among those with a late HIV diagnosis, among those who did not have a previous HIV negative test as well as among those without this information, and among those who did not have a previous diagnosis of sexually-transmitted infections (STI) or did not report this information. HBV coinfection was detected in 51.2% of persons and no differences emerged between HCV-unware and HCV-aware. No association were found by gender, place of birth, place of living, risk factors for HIV acquisition and FIB-4 score. Moreover, no significant differences in the prevalence of HCV viremia were observed (Table 1). Among those with positive viremia, the median HCV RNA level detected did not differ comparing HCV-aware and unaware persons (640,402; IQR: 190,548–2,234,779 vs 1,044,649; IQR: 260,857–3,199,032 respectively, $p = 0.256$; Mann–Whitney test). The most widespread HCV genotype, classified in 116 persons, was type 1 (53.9%) while type 3 was present in 22.4%, type 4 in 16.4% and type 2 in 3.4%. These proportions did not vary according to HCV awareness (data not shown).




| N. patients | 2004-2006 | 2007-2009 | 2010-2011 | 2012-2013 |
|---|---|---|---|---|
| IDU | 64 | 50 | 42 | 17 |
| MSM | 260 | 301 | 438 | 472 |
| Other | 256 | 348 | 355 | 324 |
| Overall | 580 | 699 | 835 | 813 |

**Fig. 2.** Anti-HCV prevalence stratified by mode of infection in persons newly diagnosed with HIV in Rome, Italy, 2004–2015. Number of enrolled patients by mode of HIV-infection and by study period are reported in the table at the bottom of the graph. IDU: Injecting drug users; MSM: Men-who-have-sex-with-Men; Other: Heterosexuals contacts/Other/Unknown.

At multivariable analysis, persons without a previous negative HIV test or for whom past test history was unknown remained at increased risk of being HCV unaware. The association with HCV unawareness was not confirmed for late HIV diagnosis and for no previous STI, while unknown previous STI remained associated with HCV unawareness.

## Discussion

Over a 12-year period, we recorded a 70.6% decrease in prevalence of anti-HCV positivity, among persons with newly diagnosed HIV infection. This observation is consistent with the decreasing trend of HCV prevalence recorded among persons entering HIV care in Italy, and may partly reflect a decrease in the proportion of injecting drug users among newly diagnosed HIV infections [11].

We observed that more than half of newly diagnosed persons were unaware of their positive HCV serostatus before HIV diagnosis, and this proportion was stable over time. This evidence, taken together with other studies [12,13], may suggest the existence of a sizeable population of persons with undiagnosed coinfection in high-income countries.

The majority of HCV-unaware individuals, for which HCV RNA was obtainable, had active HCV infection and overall almost one-fifth of them had advanced liver disease according to the FIB-4 score; these persons can be classified as having a late HCV diagnosis and are in immediate need of HCV treatment [14]. Moreover over one-half of HCV-unaware individuals had also an HBV coinfection.

In this population, unawareness of HCV infection was more common among individuals who were diagnosed late with HIV infection and had no previous STI diagnosis, and it was significantly associated at multivariable analysis with no previous HIV tests, a factor that has been found to be associated with late HIV presentation [8,15]. Interestingly, a non-negligible proportion of these who were aware of HCV positivity were tested for HIV after a median of 8.4 years; this is consistent with a previous analysis suggesting that diagnosis of HCV is in some instances a missed opportunity for an earlier HIV diagnosis [8].

A limitation of this study is that the population was recruited in a single institution, even if it accounts for 47% of the newly diagnosed HIV infections reported during the study period in our region [Regional Infectious Diseases Surveillance Unit, written communication, May 25, 2017]. Moreover, information on previous HCV diagnosis was collected through patient's interview and this may imply a recall bias; nonetheless, we have previously shown a good concordance among self-reported history of viral hepatitis and serological data in this study [8]. Finally, for staging of liver disease among anti-HCV positive individuals we used the FIB-4 score, a non-invasive test that has been specifically validated in persons co-infected with HIV. The accuracy of this test however may be influenced by a series of factors including HIV-related thrombocytopenia, and it has been shown to be inferior to that of transient elastography [16].

## Conclusions

Increasing detection and engagement in care and treatment of persons with HCV-HIV coinfection will be needed to maximize the potential benefit of new anti-HCV drugs at individual and population level. Our data suggest that integrating HCV screening into interventions aimed at promoting early HIV diagnosis may contribute to achieving these goals.

## Author contributions

PS, GI and EG designed the study and supervised data analysis. AN performed data analysis. NO, GDC, SP, CA, IM, UVC, AA and VP were involved in acquisition and/or interpretation of data. PS and EG drafted the manuscript. All authors revised the manuscript for significant intellectual content and approved the final version.

**Table 1**
Characteristics associated with unawareness of HCV serostatus among 250 anti-HCV positive individuals newly diagnosed with HIV.

| Characteristics | Unaware/total N. (%) | Univariable analysis OR[a] (95%CI[b]) | p-value | Multivariable analysis OR[a] (95%CI[b]) | p-value |
|---|---|---|---|---|---|
| Gender | | | | | |
| Female | 29/56 (51.8) | 1 | | | |
| Male | 116/194 (59.8) | 1.38 (0.76–2.51) | 0.286 | | |
| Place of birth | | | | | |
| Italy | 103/186 (55.4) | 1 | | | |
| Other | 42/64 (65.6) | 1.54 (0.85–2.78) | 0.153 | | |
| Place of living | | | | | |
| City of Rome | 101/167 (60.5) | 1 | | | |
| Metropolitan area of Rome | 28/51 (54.9) | 0.79 (0.42–1.49) | | | |
| Other | 16/32 (50.0) | 0.65 (0.31–1.39) | | | |
| Risk factors for HIV acquisition | | | | | |
| Injecting drug users | 75/138 (54.3) | 1 | | | |
| Men-who-have-sex-with-Men | 24/41 (58.5) | 1.18 (0.58–2.40) | 0.636 | | |
| Heterosexuals contacts/Other | 46/71 (64.8) | 1.54 (0.85–2.79) | 0.149 | | |
| Late HIV diagnosis | | | | | |
| No | 47/104 (45.2) | 1 | | 1 | |
| Yes | 98/146 (67.1) | 2.48 (1.47–4.16) | 0.001 | 1.42 (0.79–2.55) | 0.240 |
| HCV viremia | | | | | |
| RNA negative | 19/38 (50.0) | 1 | | | |
| RNA positive | 85/143 (59.4) | 1.46 (0.71–3.00) | 0.297 | | |
| Unknown | 41/69 (59.4) | 1.46 (0.66–3.25) | 0.348 | | |
| FIB-4 score | | | | | |
| <3.25 | 112/193 (58.0) | 1 | | | |
| ≥3.25 | 25/40 (62.5) | 1.20 (0.58–2.43) | 0.602 | | |
| Unknown | 8/17 (47.1) | 0.64 (0.24–1.74) | 0.384 | | |
| Hepatitis B core antibody | | | | | |
| Negative | 54/85 (63.5) | 1 | | | |
| Positive | 71/128 (55.5) | 0.71 (0.41–1.25) | 0.243 | | |
| Unknown | 20/37 (54.0) | 0.67 (0.31–1.48) | 0.326 | | |
| Year of HIV diagnosis | | | | | |
| 2004-2006 | 49/89 (55.1) | 1 | | | |
| 2007-2009 | 43/62 (69.3) | 1.85 (0.93–3.65) | 0.078 | | |
| 2010-2012 | 34/62(54.8) | 0.99 (0.52–1.90) | 0.979 | | |
| 2013-2015 | 19/37 (51.3) | 0.86 (0.40–1.86) | 0.704 | | |
| Previous Sexually Transmitted Infections[c] | | | | | |
| Yes | 11/31 (35.5) | 1 | | 1 | |
| No | 108/189 (57.1) | 2.42 (1.10–5.34) | 0.028 | 1.94 (0.83–4.55) | 0.128 |
| Unknown | 26/30 (86.7) | 11.82 (3.27–42.69) | <0.001 | 5.32 (1.32–21.43) | 0.019 |
| Previous negative HIV-test | | | | | |
| Yes | 50/130 (38.5) | 1 | | 1 | |
| No | 57/73 (78.1) | 5.70 (2.95–11.0) | <0.001 | 4.70 (2.36–9.35) | <0.001 |
| Unknown | 38/47 (80.8) | 6.75 (3.00–15.15) | <0.001 | 4.47 (1.90–10.51) | 0.001 |
| Age (per 1 year increase) | | 0.99 (0.96–1.01) | 0.406 | | |

[a] OR = odds ratio.
[b] CI = confidence interval.
[c] Includes HVB, syphilis, gonorrhea, genital herpes, genital condylomatosis or other STI if diagnosed before HIV diagnosis.

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## Competing interests

UVC has received personal fees for consultancy from Biotest and Abbvie, and speaker's fee from Bristol Meyer Squibb. AA has received grants, personal fees and non-financial support from Bristol Myers Squibb, grants, personal fees and non-financial support from Gilead Sciences, grants and personal fees from Janssen-Cilag, personal fees from Merck, personal fees and non-financial support from Abbvie, grants, personal fees and non-financial support from ViiV Healthcare. EG has received personal fees from Gilead Sciences, Janssen, Otsuka Novel Products and Angelini for consultancy or lectures. All other authors report no potential conflict of interest.

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## References

[1] Peters L, Klein MB. Epidemiology of hepatitis C virus in HIV-infected patients. Curr Opin HIV AIDS 2015;10:297–302, http://dx.doi.org/10.1097/COH.0000000000000183.
[2] Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis 2016;16:797–808, http://dx.doi.org/10.1016/S1473-3099(15)00485-5.
[3] Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. oral direct-acting agent therapy for hepatitis C virus infection: a systematic review. Ann Intern Med 2017;166:637–48, http://dx.doi.org/10.7326/M16-2575.

[4] Boerekamps A, van den Berk G, Lauw F, Leyten EM, van Kasteren ME, Posthouwer D, et al. Declining hepatitis C virus (HCV) incidence in Dutch human immunodeficiency virus-positive men who have sex with men after unrestricted access to HCV therapy. Clin Infect Dis 2018;17:1360–5, http://dx.doi.org/10.1093/cid/cix1007.
[5] Roberson JL, Kan VL. Hepatitis C virus continuum of care in the interferon and direct-acting agent eras among HIV-coinfected patients. AIDS Res Hum Retroviruses 2017;33:405–6, http://dx.doi.org/10.1089/AID.2016.0170.
[6] Rockstroh JK. Is hepatitis C virus elimination in well-defined patient groups possible? Clin Infect Dis 2018;17:1366–7, http://dx.doi.org/10.1093/cid/cix1010.
[7] Deuffic-Burban S, Deltenre P, Buti M, Stroffolini T, Parkes J, Mühlberger N, et al. Predicted effects of treatment for HCV infection vary among European countries. Gastroenterology 2012;143:974–85, http://dx.doi.org/10.1053/j.gastro.2012.05.054.
[8] Scognamiglio P, Chiaradia G, De Carli G, Giuliani M, Mastroianni CM, Aviani Barbacci S, et al. The potential impact of routine testing of individuals with HIV indicator diseases in order to prevent late HIV diagnosis. BMC Infect Dis 2013;13:473, http://dx.doi.org/10.1186/1471-2334-13-473.
[9] Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317–25.
[10] Antinori A, Coenen T, Costagiola D, Dedes N, Ellefson M, Gatell J, et al. Late presentation of HIV infection: a consensus definition. HIV Med 2011;12:61–4, http://dx.doi.org/10.1111/j.1468-1293.2010.00857.x.
[11] Rossetti B, Bai F, Tavelli A, Galli M, Antinori A, Castelli F, et al. Evolution of the prevalence of HCV infection and HCV genotype distribution in HIV-infected patients in Italy between 1997 and 2015. Clin Microbiol Infect 2018;24:422–7, http://dx.doi.org/10.1016/j.cmi.2017.07.021.
[12] Torian LV, Felsen U, Xia Q, Rude E, Rose H, Bocour A, et al. Undiagnosed HIV and HCV infection in a New York City emergency department, 2015. Am J Public Health 2018;108:652–8, http://dx.doi.org/10.2105/AJPH.2018.304321.
[13] Collier MG, Cuevas-Mota J, Armenta RF, Teshale EH, Garfein RS. Awareness of HCV infection among persons who inject drugs in San Diego, California. Am J Public Health 2015;105:302–3, http://dx.doi.org/10.2105/AJPH.2014.302245.
[14] Mauss S, Pol S, Buti M, Duffell E, Gore C, Lazarus JV, et al. Late presentation of chronic viral hepatitis for medical care: a consensus definition. BMC Med 2017;15:92, http://dx.doi.org/10.1186/s12916-017-0856-y.
[15] Diaz A, del Romero J, Rodriguez C, Alastrue I, Belda J, Bru FJ, et al. Effects of region of birth, educational level and age on late presentation among men who have sex with men newly diagnosed with HIV in a network of STI/HIV counselling and testing clinics in Spain. Euro Surveill 2015;20, pii: 21088.
[16] Tsochatzis EA, Castera L. Assessing liver disease in HIV-HCV coinfected patients. Curr Opin HIV AIDS 2015;10:316–22, http://dx.doi.org/10.1097/COH.0000000000000176.