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## Original article

# Prevalence and characteristics of HIV/HBV and HIV/HCV coinfections in Tuscany



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## ABSTRACT

**Introduction:** Worldwide about 30% of HIV-infected patients are coinfecting with HCV or HBV. The HIV/HCV coinfection is more common in individuals who have a history of drug addiction. The aims of this study were to assess the HCV and HBV prevalence in HIV-infected patients and analyze their characteristics.

**Methods:** We considered the new HIV diagnoses notified by the regional surveillance system of Tuscany from 2009 to 2013. Descriptive analyses were conducted on the socio-demographic characteristics, routes of transmission, and reason to perform the test. In coinfecting patients we assessed the risk for being late presenter (LP) or the risk of having AIDS.

**Results:** In 5 years of surveillance a total of 1354 new HIV diagnoses were notified: 1188 (87.7%) were HIV alone, 106 (7.8%) HIV/HCV, 56 (4.1%) HIV/HBV, and 4 (0.33%) HIV/HCV/HBV. The main risk factor was injection drug use in 52.8% of HCV/HIV cases, while in HIV/HBV patients the main risk factor was sexual exposure. HIV/HBV coinfecting patients showed worse clinical and immunological features than HIV and HIV/HCV patients: 78.6% had CD4 count less than  $350 \text{ mm}^{-3}$  (vs. 54.6% and 62.1%, respectively) and 39.4% had AIDS (vs 20.7% and 7.6%). The risk for being LP triples for HIV/HBV (OR 2.98; 95% IC: 1.56–5.70) than patients with HIV alone.

**Conclusions:** We have observed less advanced disease in HIV and HCV-HIV patients compared with HBV-HIV coinfecting patients. Moreover, our results show a higher prevalence of HIV/HCV among drug addicts and in the age-group 35–59, corresponding to those born in years considered most at risk for addiction. This study also confirms the finding of a less advanced HIV disease in HIV/HCV coinfecting patients.

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## Introduction

The Acquired Immune Deficiency Syndrome (AIDS), reported for the first time in literature in 1981, represents the final

clinical stage of infection by the human immunodeficiency virus (HIV).<sup>1</sup>

The advent of Highly Active Anti-Retroviral Therapy (HAART) has changed the natural history and epidemiology of HIV infection. In particular, the mortality rate has decreased

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as a consequence of the reduction in the number of people who develop the condition of AIDS. In 2012, people living with HIV infection or AIDS were 35 million worldwide, while the new diagnoses were about 2.3 million, with a decrease of 33% compared to 2001, when new infections were approximately 3.4 million.<sup>2</sup>

Sub-Saharan Africa is the most affected region. Recently, 1 million new diagnoses were reported. South and South-East Asia reported 270 thousand new diagnoses. In Europe, HIV infection remains a problem of major public health importance. Italy, in 2012, reported 3853 new diagnoses of HIV infection and 715 cases of AIDS, amounting to an incidence rate of 6.5 and 1.7 cases per 100,000 inhabitants, respectively. These rates, although lower than the European average, are higher than the average of other European Union and European Economic Area (EU/EEA) countries.<sup>3</sup>

Worldwide, about 1 million deaths per year are attributed to hepatitis B or C viral infections (HBV or HCV). This represents 2.7% of all cause mortality. The most common causes include hepatocellular carcinoma. Moreover, 57% of cases of liver cirrhosis and 78% of liver cancer are caused by HBV and HCV.<sup>4</sup> HBV, HCV, and HIV share the same transmission routes. It has been estimated that worldwide about 30% of people with HIV are coinfecting with HCV or HBV.<sup>5</sup> Usually, the HIV/HCV coinfection is more common in individuals who have a history of drug addiction.<sup>6</sup> Several studies have also demonstrated that such coinfections present a major risk for liver fibrosis progression and subsequent evolution to cirrhosis.<sup>7</sup>

Based on these premises, the objectives of this study were to evaluate the prevalence of HIV/HCV and HIV/HBV coinfections in Tuscany and to analyze their characteristics.

## Methods

In Italy, AIDS was declared a nationally notifiable infectious disease by Ministerial Decree No. 288 of November 28, 1986 and was subsequently subjected to special notification by filling in a special form. In 2008, new diagnoses of HIV infections were also subjected to mandatory notification.

In Tuscany, the management of the HIV regional surveillance system has been improved since 2009 and requiring notification of new HIV diagnoses.

In this study, we considered the cases of new HIV diagnoses notified in Tuscany from 2009 to 2013 to the Regional Surveillance System. This dataset contained information about patient gender, age, nationality, mode of transmission, reason for being tested, CD4 lymphocytes count, HIV viral load, and AIDS diagnosis. We analyzed the prevalence of coinfection with HBV (based on the presence of antigen surface – HBsAg), HCV (based on the presence of anti-HCV antibody, which identifies people who have been infected with the virus), or both. We considered the following clinical and immunological conditions: (1) late presentation (LP): persons presenting for care with a CD4 count below 350 cells/ $\mu$ L or with an AIDS-defining event (such as bacterial infections, candidiasis, cryptococcosis, cytomegalovirus retinitis, Kaposi sarcoma, lymphoma), irrespective of CD4 cell count; (2) presentation with advanced HIV disease (AHD): persons presenting for care with a CD4 count below 200 cells/ $\mu$ L or with an AIDS-defining

event, regardless of the CD4 cell count<sup>8</sup>; and (3) AIDS condition, defined as having HIV and an opportunistic infection, regardless of the CD4 cell count.

Socio-demographic characteristics, risk factors, reasons for being HIV tested, and the clinical and immunological features of patients were analyzed in the following four groups of patients: HIV mono-infection, HIV/HBV, HIV/HCV, and HIV/HBV/HCV infected patients. A chi-square test was performed to analyze the association between each variable and the condition of coinfection.

Multivariate logistic regression analysis was used to explore if the coinfection conditions were associated with LP, AHD or AIDS, adjusting for gender, age, nationality, and risk factors.

Statistical analyses were performed using STATA SE 12.0 statistical software.

## Results

In five years of surveillance (2009–2013), 1402 new HIV diagnoses were notified in Tuscany, with an incidence rate of 7.6 per 100,000 residents. Information on HBV or HCV coinfection was available for 1354 (96.6% of the total number of the new HIV diagnoses) HIV infected patients: 1188 (87.7%) were mono-infected, 106 (7.8%) were coinfecting with HIV/HCV, 56 (4.1%) with HIV/HBV, and 4 (0.3%) with HIV/HCV/HBV.

In the HIV mono-infected, HIV/HBV, and HIV/HCV groups 20.9%, 14.3%, and 18.9% were female, respectively (Table 1). Italian nationality was significantly different in three groups of patients: 91.5% of HIV/HCV patients, 60.7% of HIV/HBV, and 74.8% of HIV mono-infection. Most (73.6%) of the HIV/HCV patients were diagnosed in the 35–59 age group (median age 43), compared to 50.0% of HIV/HBV patients (median age 38) and 55.6% of HIV mono-infected patients (median age 39).

Among HIV/HCV cases 52.8% had been infected through injection drug use. In HIV/HBV and HIV mono-infected patients, the main risk factor for viral transmission was sexual exposure (Fig. 1).

HIV testing was mainly done due to suspicion of a disease or HIV-related clinical signs of acute infection, especially in HIV/HBV patients (62.5%). The test was performed spontaneously due to the perception of the risk of infection by 14.3% of HIV/HBV, 26.7% of HIV mono-infected, and 21.7% of HIV/HCV patients. Moreover, among HIV/HCV patients, 7.6% and 12.3% of the patients performed the test in prison or because it was offered by the Service for Drug Addiction (Table 2).

HIV/HBV patients presented a worse clinical and immunological picture compared with HIV mono-infected and HIV/HCV patients. HIV viral load of HIV/HBV and HIV/HCV coinfecting patients was not significantly different. In HIV/HBV patients the proportions of LP (78.6%) and AHD (64.3%) were higher compared to HIV/HCV (61.3% and 41.5%) and HIV mono-infected patients (55.2% and 39.6%). AIDS was diagnosed in 39.3%, 20.7%, and 7.6% of HIV/HBV, HIV mono-infected and HIV/HCV patients, respectively.

Adjusting for gender, age, nationality, and risk factors, the HIV/HBV patients showed a higher risk to be LP compared to HIV mono-infected patients (OR 3.04; 95% CI: 1.55–5.95). The risk of having AHD was also higher in HIV/HBV patients (OR 2.84; 95% CI: 1.57–5.14) compared to HIV mono-infected

**Table 1 – Socio-demographic characteristics of HIV, HIV/HBV, HIV/HCV, HIV/HCV/HBV patients notified in Tuscany (2009–2013).**

Socio-demographic characteristics	HIV		HIV/HBV		HIV/HCV		HIV/HCV/HBV		p-value
	n	%	n	%	n	%	n	%	
<b>Gender</b>									
Male	940	79.1	48	85.7	86	81.1	3	75.0	0.647
Female	248	20.9	8	14.3	20	18.9	1	25.0	
<b>Age group</b>									
0–16	4	0.3	0	–	0	–	0	–	0.050
17–34	427	35.9	21	37.5	20	18.9	1	25.0	
35–59	660	55.6	28	50.0	78	73.6	3	75.0	
≥60	97	8.2	7	12.5	8	7.6	0	–	
<b>Nationality</b>									
Italian	889	74.8	34	60.7	97	91.5	4	100.0	0.000
Foreign	299	25.2	22	39.3	9	8.5	0	–	

**Table 2 – Reasons for getting an HIV test in HIV, HIV/HBV, HIV/HCV, HIV/HCV/HBV adult patients notified in Tuscany (2009–2013).**

Reasons for getting an HIV test <sup>a</sup>	HIV	HIV/HBV	HIV/HCV
Hypothesis of an HIV-related pathology	38.2	46.4	31.1
Hypothesis of a sexually transmitted disease	9.0	12.5	4.7
Situation of acute infection	7.9	3.6	8.5
Total number tested for acute infection/STD/HIV related disease	55.2	62.5	44.3
Spontaneously	26.7	14.3	21.7
Gynecological consultation during pregnancy	4.1	3.6	2.8
Offered after informative campaign	1.9	1.8	0.9
Offered by the Service for Drug Addiction	0.9	1.8	12.3
Carried out before surgery	1.4	3.6	–
Offered in prison	0.6	1.8	7.6
Offered before blood/organ/tissue/sperm donation	1.9	1.8	–
Offered by family consultant/gynecologist (if not pregnant)	0.7	–	–
No risk factor	0.4	–	–
Other	6.0	7.1	10.4

<sup>a</sup> Multiple responses.

patients. No statistically significant difference was found between HIV/HCV and HIV monoinfected patients (Table 3). Compared to HIV monoinfected patients, HIV/HBV patients had a higher risk of AIDS (OR 2.44; 95% CI: 1.35–4.43) while the risk of HIV/HCV patients seemed lower (OR 0.23; 95% CI: 0.10–0.52).

## Discussion

To our knowledge, this study shows for the first time that the clinical and immunological features of HIV/HBV coinfecting

patients are more severe compared to those co-infected with HIV/HCV and HIV monoinfected patients at the time of HIV diagnosis. HIV was diagnosed either in prison or by the Service for Drug Addiction in almost 20% of HCV/HIV coinfecting patients, which may have contributed to the less advanced HIV disease in this population. In fact, drug use is the main risk factor for transmission in this group of patients. Moreover, about 15–45% positive for anti-HCV antibodies spontaneously clear the virus.

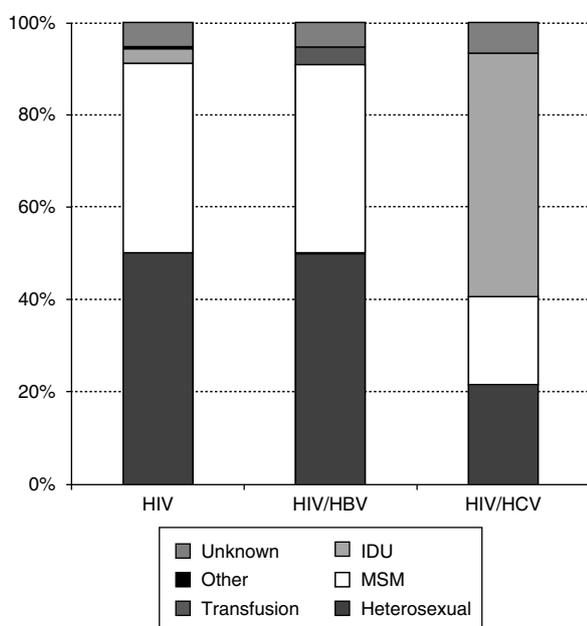
The HIV/HBV co-infection was common in foreigners and they had both age and risk factors similar to those who

**Table 3 – Multivariate logistic regression analysis. Estimate of relative risk for HIV, HIV/HBV, HIV/HCV to be LP, AHD or AIDS. Adult patients notified in Tuscany, 2009–2013.**

	Late presenter			Advanced HIV disease			AIDS		
	% <sup>a</sup>	OR	IC 95%	%	OR	IC 95%	%	OR	IC 95%
HIV	55.2	1.00	–	39.6	1.00	–	20.7	1.00	–
HIV/HBV	78.6	3.04	1.55–5.95	64.3	2.84	1.57–5.14	39.3	2.44	1.35–4.43
HIV/HCV	61.3	1.24	0.75–2.05	41.5	0.81	0.49–1.34	7.6	0.23	0.10–0.52

Odds ratio and confidence intervals at 95% adjusted by gender, age, nationality, mode of transmission.

<sup>a</sup> The total amount of the three conditions is not 100%, because each group may be inside other groups.



**Fig. 1 – HIV transmission route in HIV, HIV/HBV, HIV/HCV, HIV/HCV/HBV infected adult patients notified in Tuscany (2009–2013).**

were HIV monoinfected. However, these patients had a worse immunological picture at the time of HIV diagnosis compared to HIV/HCV co-infected patients, probably because the sexual transmission was the main risk factor in HIV/HBV coinfecting patients, with subsequent less perception of the infection transmission risk, therefore they only performed the test after experiencing HIV-related symptoms. Moreover, they were at higher risk of having LP, AHD, or AIDS compared to HCV coinfecting patients. According with these findings, recent studies pointed out that HBV infection complicates the management of HIV infection. In fact, patients with chronic HBV at the time of HIV diagnosis had an impaired CD4 recovery, an accelerated immunologic deterioration, and a significantly higher risk of an AIDS or death event.<sup>9,10</sup> This is similar to HIV induced impairment of HBV, which in turn influences negatively the course and progression of HIV disease.

We also found a high prevalence of HBV–HIV coinfection in foreigners. In 1991, Italy initiated universal HBV vaccination for all newborns and 12-year-old adolescents. Since the vaccination programs had a different pace in developing countries, the high prevalence among foreigners could be due to non-compliance with Italy's vaccination program.<sup>11</sup>

The introduction of blood-screening for HCV in the early 1990s strongly decreased HCV transmission from blood transfusions. Our data also confirm the results of several studies that showed a high prevalence of HCV coinfection in HIV-infected intravenous drug users.<sup>6,12,13</sup> Moreover, this coinfection was more prevalent in patients aged 35–59 years, corresponding to those born in the years at major risk for drug abuse. Baby boomers are people born during the post-World War II, approximately between the years of 1946 and 1964. HCV infection and fatty liver disease are more common in the Baby Boomers and may play a more dominant role as they age,<sup>14</sup> probably because aging of the baby boomer cohort will soon

comprise a large proportion of persons who have used illicit drugs in their lifetimes. A recent cross-sectional study conducted in Brazil showed that the prevalence rate of HIV-HCV coinfection was 6.9% among 848 HIV-infected patients receiving care at reference centers in the Midwest Region of Brazil.<sup>15</sup> This also confirms the less advanced disease in these patients, probably due to a higher perceived risk of disease, which could lead them to test earlier. Even after adjusting for gender, age, nationality, and transmission route, we were able to show that HIV/HCV had a lower risk of having AIDS diagnosis at the time of detection of HIV infection compared to HIV monoinfected patients.

HCV screening in HIV-infected patients is highly recommended in order to treat HCV infection when appropriate. Currently, interferon-free treatment regimens are available and they require shorter periods of treatment (3 months). These regimens are free of the associated substantial side effects, and preliminary results suggest that these treatments are also effective in patients with cirrhosis (some for 6 months).<sup>16</sup>

In conclusion, our data show that both age and risk factors for HIV/HBV coinfecting patients are similar to that of HIV monoinfected patients. Moreover, the prevalence of HBV was higher in HIV-infected foreigners compared to HIV-infected Italian patients. Future pathogenesis studies are needed to confirm the higher risk for LP, AHD, and AIDS in HBV coinfecting patients. Our data also confirm a higher prevalence of HIV/HCV infections among drug addicts, especially in the 35–59 age group, corresponding to those born in the years considered most at risk for drug abuse. This also suggests that the higher perceived risk of disease leads to earlier HIV testing compared to HIV/HBV patients.

## Conflicts of interest

The authors declare no conflicts of interest.

## REFERENCES

1. EPICENTRO. Infezione da HIV e AIDS; 2014. Available from: <http://www.epicentro.iss.it/problemi/aids/storia.asp>
2. World Health Organization. Global report: UNAIDS report on the global AIDS epidemic 2013; 2013. Available from: [http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/unaids\\_global\\_report\\_2013\\_en.pdf](http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/unaids_global_report_2013_en.pdf)
3. Centro Operativo AIDS. Aggiornamento delle nuove diagnosi di infezione da HIV e dei casi di AIDS in Italia al 31 Dicembre 2012. *Notiziario dell'Istituto Superiore di Sanità* 26(9); 2013.
4. World Health Organization. Hepatitis: frequently asked questions; 2014. Available from: [http://www.who.int/csr/disease/hepatitis/world\\_hepatitis\\_day/question\\_answer/en/](http://www.who.int/csr/disease/hepatitis/world_hepatitis_day/question_answer/en/)
5. Lacombe K, Rockstroh J. HIV and viral hepatitis coinfections: advances and challenges. *Gut*. 2012;61:i47–58.
6. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol*. 2006;44:S6–9.
7. Chen JY, Feeney ER, Chung RT. HCV and HIV co-infection: mechanisms and management. *Nat Rev Gastroenterol Hepatol*. 2014;11:362–71.
8. Antinori A, Coen T, Costagiola D, et al. Late presentation of HIV infection: a consensus definition. *HIV Med*. 2011;12:61–4.

9. Chun HM, Roediger MP, Hullsiek KH, et al. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. *J Infect Dis.* 2012;205:185-93.
10. Tsai MS, Chang SY, Lo YC, et al. Hepatitis B virus (HBV) coinfection accelerates immunologic progression in patients with primary HIV infection in an area of hyperendemicity for HBV infection. *J Infect Dis.* 2013;208:1184-6.
11. Stasi C, Silvestri C, Bravi S, et al. Hepatitis B and C epidemiology in an urban cohort in Tuscany (Italy). *Clin Res Hepatol Gastroenterol.* 2015;39:e13-5.
12. Amon JJ, Garfein RS, Ahdieh-Grant L, et al. Prevalence of hepatitis C virus infection among injection drug users in the United States, 1994-2004. *Clin Infect Dis.* 2008;46:1852-8.
13. Burton MJ, Reilly KH, Penman A. Incarceration as a risk factor for hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection in Mississippi. *J Health Care Poor Underserved.* 2010;21:1194-202.
14. Davis GL, Roberts WL. The healthcare burden imposed by liver disease in aging Baby Boomers. *Curr Gastroenterol Rep.* 2010;12:1-6.
15. Freitas SZ, Teles SA, Lorenzo PC, et al. HIV and HCV coinfection: prevalence, associated factors and genotype characterization in the midwest region of Brazil. *Rev Inst Med Trop Sao Paulo.* 2014;56:517-24.
16. Stasi C, Silvestri C, Voller F, Cipriani F. The epidemiological changes of HCV and HBV infections in the era of new antiviral therapies and the anti-HBV vaccine. *J Infect Public Health.* 2015. pii:S1876-0341(15)00101-X.