Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2026;35:33-36
doi: 10.15570/actaapa.2026.2

Trends and determinants of hepatitis C virus infection among people living with HIV in Slovenia: a nationwide study, 1986–2024

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Abstract

Introduction: Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) share transmission routes and cause significant morbidity and mortality worldwide. Three previous nationwide studies reported a low prevalence of HCV infection among Slovenian people living with HIV (PLWH).
Methods: Data were collected de novo from 526 PLWH newly diagnosed with HIV in Slovenia between January 1st, 2014, and December 31st, 2024, and combined with data from previous studies on this topic.
Results: Altogether 1,085 (93%) PLWH were tested for HCV at HIV diagnosis: 82 (7.6%) had anti-HCV antibodies (49 or 59.8% of them viremic), and three had HCV RNA only, resulting in an HCV prevalence of 7.8%. A significant increase in the prevalence of HCV infection has been observed over the last decade. HCV infection was significantly associated with female sex, foreign nationality, parenteral HIV transmission route, and non-B HIV subtype. The most frequent HCV genotypes were 1 (60%), 3 (22%), and 4 (16%), markedly different than previously found in the general population.
Conclusions: The overall prevalence of HCV infection among PLWH in Slovenia remains low, but a significant increase has been observed in the last decade compared to the previous one. Such a situation requires further regular and tight monitoring to allow timely interventions if and when needed.

Keywords: HIV, hepatitis C, prevalence, Slovenia

Received: 27 November 2025 | **Returned for modification:** 13 January 2026 | **Accepted:** 23 January 2026

Introduction

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) share transmission routes and cause significant morbidity and mortality worldwide. The interaction between HIV and HCV affects the transmission and natural course of HCV infection. HCV infection in people living with HIV (PLWH) results in a lower rate of spontaneous clearance of HCV, faster liver disease progression, and a more aggressive course of liver disease (1, 2). After implementation of direct-acting antivirals (DAAs), the World Health Organization (WHO) announced ambitious viral hepatitis elimination goals to be achieved by 2030 (3). To contribute to these WHO goals, a comprehensive review was recently published to assess the current situation in Europe and address some knowledge gaps. The prevalence of chronic HCV infection in the European Union (EU) / European Economic Area (EEA) was estimated at 0.5% in 2019, with at least 36% of infections attributable to transmission among people who inject drugs (PWID) (4). In addition, higher hepatitis C prevalence was found among PLWH compared to HIV-negative individuals in different geographical regions and with different transmission risks; however, it was most pronounced among PWID, emphasizing the importance of HCV testing among PLWH (2).

Slovenia, a small central European country with 2.1 million inhabitants, has a very low HIV population prevalence, with a current estimate of fewer than 1,000 PLWH in the country, most of whom are men who have sex with men (MSM). Only 14 of the 433 (3.2%) PLWH newly diagnosed from 2014 to 2023 were PWID, five of whom reported injecting drugs abroad (5). Similarly, a low population prevalence of HCV infection of 0.07% was estimated in 2019, one of the lowest in Europe, with at least 84% attributable to PWID (4). Three previous nationwide studies in Slovenia reported a prevalence of HCV infection of 16.9%, 10.7%, and 7.6% among Slovenian PLWH diagnosed in 1986–2000, 1986–2008, and 1986–2013, respectively. The aim of this nationwide study was to update the estimate of HCV prevalence in Slovenian PLWH at HIV diagnosis, to determine the variables associated with HCV positivity, and to analyze prevalence trends over the last 4 decades.

Methods

For this study, data were collected de novo from 526 PLWH newly diagnosed with HIV in Slovenia between January 1st, 2014, and December 31st, 2024, and combined with existing data extracted from previous studies on the same topic (6–8).

HCV-positive status was defined as the presence of anti-HCV antibodies or HCV RNA at the time of HIV diagnosis, determined using several generations of commercial anti-HCV and HCV RNA assays. For HCV RNA-positive PLWH, information on HCV genotype was also retrieved from the national database, and, in cases with virologically confirmed HCV reinfection, the most recent HCV genotype result was used for the purposes of this study. In addition, all anti-HCV-negative samples obtained from PLWH in the last 2 decades were routinely tested for the presence of HCV RNA using a mini-pool screening algorithm to detect potential cases of acute hepatitis C, which could be missed by screening using only the anti-HCV approach (9, 10). HCV infections that occurred after HIV diagnosis were not considered in this study. Epidemiological and HIV sequencing data were obtained from the HIV transmitted

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drug resistance surveillance studies (Medical Ethics Committee, Ministry of Health of Slovenia; approval ref. nos. 26/12/03 and 0120-177/2024-2711-3) (11–13).

Statistical analyses were performed using R (version 4.4.3; R Core Team, Vienna, Austria) in RStudio (version 2024.12.1). Categorical variables were compared using Pearson's chi-square test or Fisher's exact test if the expected cell count was < 5. Independent samples *t*-tests or Wilcoxon rank-sum tests were used for continuous variables. The choice of statistical test was made using a custom function that assessed distributional assumptions and expected frequencies in R. A Cochran–Armitage trend test was performed to assess changes in HCV positivity over 5-year intervals.

Results

By the end of 2024, a total of 1,165 PLWH were reported cumulatively in Slovenia. The majority were men (994; 87%) with a mean age (± standard deviation) at HIV diagnosis of 38.6 ± 11.8 years. Most PLWH with available epidemiological data reported Slovenian nationality (81%) and most (70%) were MSM. HIV subtype information was available for 649 (60%) persons, and most were infected with subtype B (79%).

Altogether, 1,085 (93%) Slovenian PLWH were tested for past and active HCV infection by detecting anti-HCV and/or HCV RNA at the time of HIV diagnosis. Of these, 82 (7.6%) had anti-HCV antibodies, and 49 of them (59.8%) were also HCV RNA positive. A further three cases were HCV RNA positive only, indicating early HCV infection at the time of testing, adding to the overall prevalence of HCV infection among PLWH to 7.8% (85/1,085; Table 1).

A significant increase in HCV positivity at HIV diagnosis was observed in the last two 5-year intervals (chi-square test for trend in proportions; $x^2 = 11.957$, df = 1, *p*-value = 0.0005; Fig. 1). Only a small portion of samples (35%) were tested for HCV retrospectively in PLWH diagnosed before 1995, making HCV prevalence data for the period from 1985 to 1994 unreliable. On the other hand, over 94% of PLWH diagnosed after this period were tested for HCV infection at all 5-year intervals. The portion of HCV-positive PLWH diagnosed from 1995 to 1999 was relatively high (22.4%), largely due to patients with hemophilia (41%; 9/22). A significant decrease in HCV positivity was observed from 22.4% in 1995–1999 to 4.6% in 2000–2004. Thereafter, the proportion remained low (below 5%) until it recently rose again to 11.9% in 2020–2024 (Fig. 1). Information on the most likely route of HIV transmission was available for 20 of the 26 HCV-positive PLWH newly diagnosed with HIV between 2020 and 2024, and, of these, 45% (9/20) were PWID. At least a quarter (7/26) of HCV-positive PLWH diagnosed between 2020 and 2024 were from Ukraine.

HCV infection in PLWH was significantly associated with female sex, foreign nationality, non-sexual route of HIV transmission (PWID and hemophilia), and non-B HIV subtype (Table 1). Specifically, of the 893 PLWH that reported the most likely route of HIV transmission, 40 reported the parenteral route (25 PWID and 12 that received clotting factor replacement for hemophilia). Among these, 37 (92.5%) were HCV positive. On the other hand,

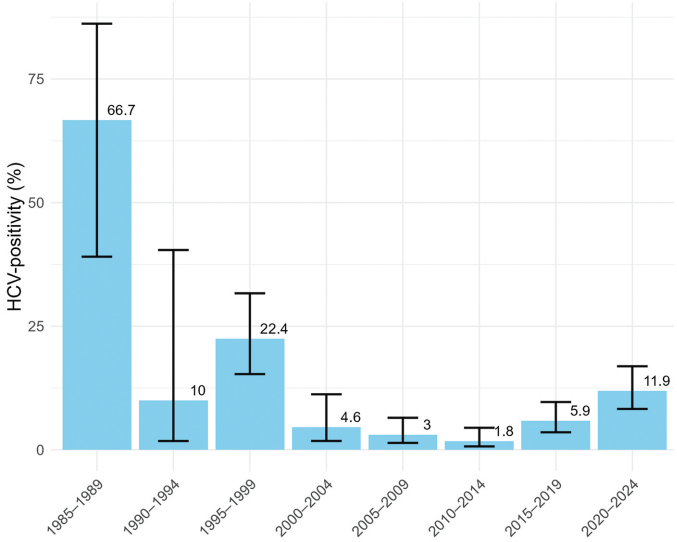

Figure 1 | Portion (with 95% confidence intervals) of hepatitis C virus (HCV) positivity by 5-year intervals of HIV-diagnosis among people living with HIV in Slovenia.

Table 1 | Characteristics of hepatitis C virus (HCV)-positive (anti-HCV and/or HCV RNA-positive) and HCV-negative people living with HIV at HIV diagnosis in Slovenia, 1986–2024.

	HCV positive	%	HCV negative	%	*p*-value
Subjects	85	7.8	1,000	92.2	
Sex					0.002
Male	63	74.1	881	88.1	
Female	22	25.9	117	11.7	
Transgender	0	0.0	2	0.2	
Age at HIV diagnosis (mean, years ± *SD*)	36.6 ± 9.9		38.6 ± 11.6		0.200
Nationality					< 0.001
Slovenian	22	25.9	564	56.4	
Other	16	18.8	119	11.9	
Unknown	47	55.3	317	31.7	
Route of HIV transmission					< 0.001
MSM	15	17.6	617	61.7	
Heterosexual contact	17	20.0	204	20.4	
PWID	25	29.4	3	0.3	
Person with hemophilia	12	14.1	0	0.0	
Other	0	0.0	10	1.0	
Unknown	16	18.8	166	16.6	
HIV subtype					0.002
B	22	25.9	489	48.9	
Non-B	16	18.8	122	12.2	
Unknown	47	55.3	389	38.9	

SD = standard deviation, MSM = men who have sex with men, PWID = people who inject drugs, HCV = hepatitis C virus.

only 3.8% of PLWH that most probably acquired HIV via the sexual route were HCV positive.

HCV genotype information was available for 50 PLWH. The most frequently detected HCV genotype was genotype 1 (60%), followed by genotype 3 (22%) and genotype 4 (16%; Fig. 2).

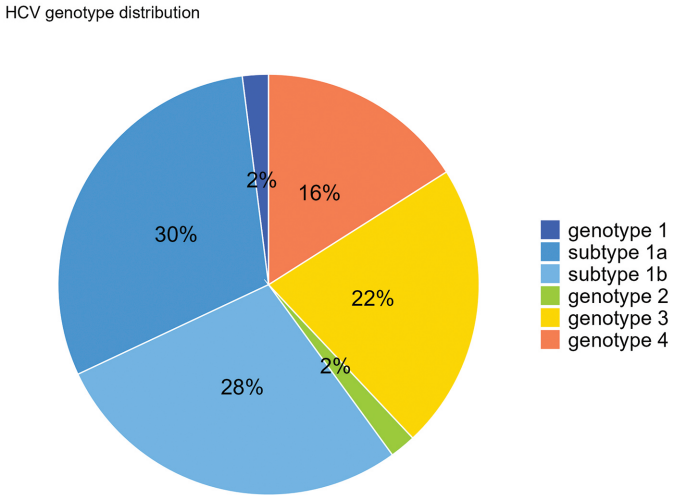

Figure 2 | Distribution of hepatitis C virus genotypes determined in people living with HIV in Slovenia, 1986–2024.

Discussion

This study provides an update on HCV prevalence at HIV diagnosis among more than 90% of all PLWH diagnosed in Slovenia by the end of 2024. The overall HCV prevalence during the study period was estimated at 7.8%. The results of this study are comparable to the 7.6% prevalence observed in the last published update, which included 91% of all PLWH diagnosed in Slovenia by the end of 2013, and to the 6.2% observed in a meta-analysis based on studies published from 2002 to 2015 among PLWH worldwide (2, 8). However, the overall HCV prevalence found in Slovenia in this study was lower than the estimated 10% and 40% found among PLWH in western/central Europe and in eastern Europe / Central Asia, respectively (2).

Screening for HCV infection in the immunocompetent population outside blood transfusion settings is usually performed with an anti-HCV test. However, the algorithm implemented in our laboratory in 2004 allows detection of acute HCV cases because all samples that test anti-HCV negative are additionally tested for HCV RNA using a 24 mini-pool strategy. This has been rationalized due to the long incubation period of HCV and the high HCV viraemia in the acute phase of infection and has been shown to be effective in detecting a number of acute HCV infections in previous studies (9, 10). In this study, three HCV RNA-positive / anti-HCV-negative cases were identified, accounting for 3.5% of all HCV-positive PLWH, a proportion that is double that of the 1.8% found in the general HCV-positive population in Slovenia (10). The results of this study additionally support the use of the mini-pool HCV RNA testing algorithm in anti-HCV negative individuals, particularly PLWH.

HCV positivity among PLWH in this study was significantly associated with female sex, foreign nationality, parenteral route of HIV transmission (PWID and hemophilia), and non-B HIV subtype. Previous studies have shown that PWID are particularly likely to be infected with HCV, with an HCV prevalence of up to 96% (2). HCV infections are still associated with injecting drug use in Europe and especially in Slovenia (4). This is also evident in this study, in which nine out of 10 PLWH that had acquired HIV via the parenteral route also tested HCV positive at HIV diagnosis, in contrast to only one out of 27 PLWH that had acquired HIV via the sexual route. Although HIV/HCV coinfection is strongly associated with PWID, fortunately, no spillover of the HIV epidemic to the PWID community has been observed in Slovenia to date (5).

Slovenia introduced screening of blood donors for anti-HCV in 1993 and for HCV RNA in 2000 (14). The higher prevalence of HIV/HCV coinfection at the beginning of the HIV pandemic is therefore probably due to the receipt of contaminated blood products before the introduction of blood donor screening, when the most affected patient group was individuals with hemophilia. A significant decline in HCV positivity among PLWH was observed in Slovenia after the introduction of HCV screening of blood donors. HCV prevalence among PLWH remained stable and below 5% from 2000 to 2014, but an increase has recently been observed, reaching 12% from 2020 to 2024. This increase is to some extent attributable to migrants, particularly from Ukraine. This is also supported by the finding of a significant association of HCV positivity with foreign origin and non-B HIV subtype in this study. Non-B subtypes were observed in less than 20% of HCV-negative PLWH, compared to 42% of HCV-positive PLWH. A previous study found a significant association of non-B subtypes in Slovenia with eastern European or African origin, heterosexual transmission, and HIV infection acquired in eastern Europe, Africa, or Asia (15).

The HCV genotype distribution among PLWH in this study differs substantially from a recent study that analyzed HCV genotype distribution in the general population in Slovenia from 2004 to 2024 (16). In this study, more genotype 1 (60%) and less genotype 3 (22%) was detected in PLWH, compared to almost identical proportions in the general population (49% and 46%, respectively). In addition, genotype 4 was detected in 16% of PLWH, but only in 1.5% of the HCV-positive total population (16).

Conclusions

Our study showed that, although the overall prevalence of HCV infection among PLWH in Slovenia remains low, a significant increase in prevalence has been observed in the last decade compared to the previous decade. Such epidemiological situation requires further regular and tight monitoring to allow timely interventions if and when needed.

Funding

This work was funded by the Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana (internal funding), and by the Slovenian Research and Innovation Agency (ARIS; funding grant no. P3-0083).

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