



Incidence of sexually transmitted hepatitis C virus infection among men who have sex with men in Japan from 2009 to 2023

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Abstract

Although the prevalence of hepatitis C virus (HCV) infection has decreased significantly with the advent of direct-acting antiviral agents, HCV is known to spread as a sexually transmitted disease among men who have sex with men (MSM), and this study aims to provide a perspective on the future prevalence of HCV in Japan. We examined incidence in two groups of MSM with HIV attending our institution in this retrospective cohort study, from 2009 to 2019 and from 2020 to May 2023 and investigated their background factors. Twenty-two cases were newly confirmed to be HCV infection in 2009–2019 and a total of 9 cases in 2020–2023, with an incidence rate of 5.04 per 1000 person-years in 2009–2019 and 5.55 per 1000 person-years in 2020–2023. All of them were diagnosed at routine outpatient visits for HIV, and few cases were considered to have symptoms of suspected hepatitis that led to a visit to the hospital and a diagnosis of HCV. Although HCV is still prevalent among MSM in Japan, it is possible that it would not have been diagnosed without testing at regular visits as in the case of people with HIV, and that the true prevalence rate among MSM, including non-HIV-infected persons, may be much higher.

KEYWORDS

HCV, hepatitis C, HIV, men who have sex with men, sexually transmitted disease

The prevalence of chronic hepatitis C and hepatitis C virus (HCV) carriers has decreased significantly in Japan due to the widespread use of direct-acting antivirals (DAA) treatment and the almost complete absence of acute hepatitis C caused by blood transfusions, needlestick injuries, and mother-to-child transmission.¹ Because of a significant decrease in the size of the population of potential reservoirs of infection, the prevalence of HCV is expected to decline further in the future.² However, in the field of medical care for people with HIV (PWH), it is known that sexually transmitted HCV

infection is prevalent among men who have sex with men (MSM).^{3,4}

The purpose of this study is to examine the incidence of HCV infection, patient backgrounds, and diagnostic opportunities, and to provide a perspective on the future HCV epidemic in Japan.

This study was a retrospective cohort study of MSM who attended IMSUT hospital, the Institute of Medical Science, the University of Tokyo, for HIV treatment and underwent blood tests between 2009 and 2023. The incidence of acute HCV infection was calculated for Group 1 from 2009 to 2019 and for Group 2 from 2020 to May 2023,

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which is after the COVID-19 epidemic. New HCV infection was defined as anti-HCV antibodies becoming positive from negative at baseline, HCV-RNA becoming positive from negative at baseline in case of reinfection. The incidence rate per 1000 person-years was calculated from the date of the first blood test to the date of the last blood test during the defined study periods. The observation period was not censored even if a new HCV infection was confirmed, because reinfection and superinfection of HCV carriers can occur. By reviewing clinical records, we retrospectively investigated age at the time of HCV infection, the results of anti-Treponema pallidum antibody and anti-hepatitis B core antibody right before HCV infection was confirmed, presence of subjective symptoms of acute hepatitis C, and reasons that led to the diagnosis of new HCV infection. The Mann-Whitney *U* test was used to test for differences in median values such as age, the fisher's exact test was used to test for differences in factors presented as percentages, and the binomial test with mid-*p* adjustment was used to test for differences in the incidence rates. The Poisson distribution of person-time were calculated using R version 4.3.1. Statistical significance was defined as two-sided *p* < 0.05 and 95% confidence interval (CI) were given where appropriate.

In 2009–2019 (Group 1), 624 (4361 person-years) were observed and in 2020–2023 (Group 2), 565 (1621 person-years) were observed. Groups 1 and 2 have 517 overlapping participants, i.e., approximately 92% of Group 2 continued to participate from the Group 1 period, suggesting that there is no difference in background factors between the two cohorts of different time periods. Median (interquartile range [IQR]) observation periods were 8.6 (3.6–10.4) years in Group 1 and 3.1 (2.9–3.2) years in Group 2. During the period, 22 cases were newly confirmed to be infected with HCV in 2009–2019 and a total of 9 cases in 2020–2023, with an incidence rate (95% CI) of 5.04 (3.16–7.63) per 1000 person-years in 2009–2019 (Group 1) and 5.55 (2.54–10.5) per 1000 person-years in 2020–2023 (Group 2), as summarized in Table 1. Reinfection after cure and superinfection of HCV carriers were also included in the outcome as new HCV infection, but the latter was not observed. Reinfection was observed in three patients (two cases in Group 1 and one case in Group 2). Overall, median age was 44 (IQR: 39–47) and 97% (30/31) were on antiretroviral therapy, 84% (26/31) were anti-Treponema pallidum (TP) antibody positive and 74% (23/31) were anti-hepatitis B core antibody positive before new HCV infection. Clinical

TABLE 1 Background of new cases of hepatitis C virus infection from 2009 to May 2023.

	Total	Group 1 (2009–2019)	Group 2 (2019–2023)	<i>p</i> value
Number of patients, <i>n</i>	31	22	9	
Incidence rate, per 1000 person-years (95% CI)	5.18 (3.52–7.36)	5.04 (3.16–7.63)	5.55 (2.54–10.5)	0.79 ^a
Age, median (IQR) ^b	44 (39–47)	44 (38–46)	45 (40–49)	0.33 ^c
Anti-TP positive, <i>n</i> (%) ^b	26 (84)	19 (86)	7 (78)	0.6 ^d
Anti-HBc or HBsAg positive, <i>n</i> (%) ^b	23 (74)	17 (77)	6 (67)	0.66 ^d
ALT > 100 IU/L, <i>n</i> (%) ^b	27 (87)	19 (86)	8 (89)	0.99 ^d
ALT > 400 IU/L, <i>n</i> (%) ^b	23 (74)	18 (82)	5 (56)	0.18 ^d
Subjective symptoms of hepatitis, ^e <i>n</i> (%)	14 (45)	11 (50)	3 (33)	0.46 ^d
No subjective symptoms and elevated ALT, <i>n</i> (%)	3 (9.7)	3 (14)	0	0.54 ^d
Reason for HCV testing, <i>n</i> (%)				
Subjective symptoms of hepatitis ^e	4 (13)	4 (18)	0	0.30 ^f
Elevated ALT	22 (71)	13 (59)	9 (100)	
Screening or health check	5 (16)	5 (23)	0	
Serotype or genotype, ^g <i>n</i> (%)				
Serotype 1 or genotype 1b	22 (73)	15 (71)	7 (78)	0.69 ^d
Serotype 2 or genotype 2A	8 (27)	6 (29)	2 (22)	0.68 ^d

Abbreviations: ALT, alanine transaminase; CI, confidence interval; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; IQR, interquartile range; TP, Treponema pallidum.

^abinomial test with mid-*p* adjustment.

^bValues at the time of HCV infection.

^cMann-Whitney *U* test.

^dFisher's exact test.

^eFatigue, loss of appetite, jaundice.

^fFisher's exact test comparing patients tested for subjective symptoms of hepatitis with patients tested for reasons other than subjective symptoms.

^gNo data available for one case.

symptoms included a maximum alanine transaminase (ALT) level of 400 IU/L or higher in 74% (23/31) of cases and subjective symptoms of hepatitis (i.e., fatigue, anorexia, and jaundice) in 45% (14/31). None of the patients had subjective symptoms or ALT findings in 9.7% (3/33). In 71% (22/31) of the cases, anti-HCV antibody testing was performed due to elevated ALT in blood tests to monitor HIV status, confirming HCV infection; in 16% (5/31) of the cases, new HCV infection were confirmed by performing anti-HCV tests for health check or other screening purposes. Only four cases were diagnosed with acute hepatitis C due to subjective symptoms of fatigue and anorexia after visits other than for routine monitoring. In 6.4% (2/31) of the cases did the virus spontaneously disappear during the acute hepatitis phase; all other cases were persistent infections lasting more than 6 months.

New HCV infections have been occurring consistently since 2009 and have maintained the same trend with a slight increase since the COVID-19 epidemic. This is consistent with the fact that the prevalence of sexually transmitted diseases (STDs) such as syphilis has been increasing in Japan,^{5,6} but considering that the number of HCV carriers in the general population has decreased dramatically since 2015 due to the spread of DAA and that mother-to-child transmission and transmission via blood products have disappeared, it means that new HCV infection is now mainly acquired as an STD.

The demographics of the cases were not significantly different between the two periods, but there were many anti-TP positive and anti-hepatitis B core antibody-positive cases overall, which can be said to be common among sexually active MSM. Some patients newly infected with HCV were presumed to be substance abusers, so "chemsex" would also be a risk factor.⁷

Symptoms of acute hepatitis C were found in more than half of the cases, but most of them were detected either during a routine visit for HIV or after anti-HCV antibody screening tests for other purposes; therefore, it is likely that many of the patients in this study with newly confirmed HCV infection would not have been diagnosed with HCV infection if they had not attended the hospital for HIV and had not had a primary care physician. HCV, like other STDs, can be detected in the same way in sexually active MSM, regardless of whether they are PWH or not. We need to think about how to improve the access to medical care among the sexually active MSM who do not have a regular doctor to consult and who do not have many opportunities to see a health care provider, and how to increase their opportunities for STD testing. Not only for HCV, but likewise for all STDs, sexually active MSM are at the same increased risk of STDs regardless of whether or not they are PWH, and are likely to remain undiagnosed.^{8,9} HIV postexposure prophylaxis (PrEP) is becoming more widespread worldwide, and the number of HIV-PrEP users is increasing in Japan.¹⁰ Increasing opportunities for hospital visits and testing for STDs would lead to the uncovering of undiagnosed STDs.⁹⁻¹¹ Therefore, physicians need to be made widely aware of the need to consider HCV as an STD.

One limitation of this study is that it is a retrospective cohort study and the observation period is the time during which blood tests

were performed, not necessarily the time during which HCV antibody testing was performed. As we have shown that elevated liver transaminases triggered the further investigations for HCV, we believe that the time of blood tests are more appropriate than the time of the antibody test. A single-center retrospective cohort study conducted between 2005 and 2012 reported an HCV infection rate of 9.35 per 1000 person-years among HIV-infected MSM, which was higher than our results.¹² This is probably due to differences in the study period and the definition of the observation period.

In this study, about 10% of newly diagnosed HCV infections were reinfection. Given that immunity to prevent HCV infection cannot be acquired by natural infection or vaccines, HCV will continue to be prevalent as an STD among MSM in the future.

AUTHOR CONTRIBUTIONS

Eisuke Adachi: carried out the project and drafted the manuscript. **Makoto Saito:** revised the manuscript. **Eisuke Adachi and Makoto Saito:** performed the statistical analysis. **Eisuke Adachi, Makoto Saito, Tadashi Kikuchi, Kazuhiko Ikeuchi, Michiko Koga, Takeya Tsutsumi, and Hiroshi Yotsuyanagi:** were responsible for the clinical management of the patient. All authors approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Ethics approval was granted by the ethics board of the Institute of Medical Science, University of Tokyo (2022-48-1128).

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