# HCV Genotype Distribution Among People Who Inject Drug in Turkey: Findings from Multicenter and Cross-Sectional Study

Substance Abuse: Research and Treatment
Volume 17: 1–6

DOI: 10.1177/11782218231157340



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**ABSTRACT**

**BACKGROUND:** Hepatitis C virus (HCV) infection is very common in people who inject drugs (PWID). Studies about the prevalence and genotype distribution of the HCV among PWID are very crucial for developing strategies to manage HCV infection. This study's objective is to map the distribution of HCV genotypes among PWID from various regions of Turkey.

**METHOD:** This prospective, multicenter, cross-sectional study involved 197 PWID who tested positive for anti-HCV antibodies from 4 different addiction treatment facilities in Turkey. Interviews were done with people who had anti-HCV antibodies, and blood samples were taken to check the HCV RNA viremia load and genotyping.

**RESULTS:** This study was conducted on 197 individuals with a mean age of 30.3 ± 8.6 years. 9.1% (136/197 patients) had a detectable HCV-RNA viral load. Genotype 3 was the most commonly observed genotype by 44.1%, followed by genotype 1a by 41.9%, genotype 2 by 5.1%, genotype 4 by 4.4%, and genotype 1b by 4.4%. Whereas genotype 3 was dominant with 44.4% at the central Anatolia region of Turkey, the frequencies of genotypes 1a and 3, which were predominantly detected in the south and northwest regions of Turkey, were very close to each other.

**CONCLUSION:** Although genotype 3 is the predominant genotype in the PWID population in Turkey, the prevalence of HCV genotype varied across the country. To eliminate HCV infection in the PWID, treatment and screening strategies that differ by genotype are essentially required. Especially identification of genotypes will be useful in developing individualized treatments and determining national prevention strategies.

**KEYWORDS:** HCV, PWID, genotype

**RECEIVED:** September 17, 2022. **ACCEPTED:** January 29, 2023.

**TYPE:** Original Research

**FUNDING:** The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Gilead Sciences İlaç San. Tic., Turkey

**DECLARATION OF CONFLICTING INTERESTS:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Introduction

Hepatitis C virus (HCV) has constituted a huge public health problem worldwide by causing liver failure, cirrhosis, hepatocellular carcinoma, and acute and chronic Hepatitis C infections with a course of high mortality. The main mechanisms of transmission are transfusion of contaminated blood and blood products, injectable drug usage, surgical procedures, and other interventional procedures. Since safe transfusion practices have been established over the past 20 years, injecting medications, particularly in developed countries, is now the primary method of HCV transmission.[1-3] While anti-HCV antibody prevalence ranges between 1.3% and 3.5% in the prevalence studies conducted with general population worldwide,[4-7] anti-HCV antibody prevalence mean is shown as 39.2% to 52.3% in the studies conducted with patient group with injecting drug use (PWID).[8-11] Anti-HCV antibody mean was found as 1.1% in the studies conducted with general population in Turkey in previous years[12] whereas anti-HCV antibody prevalence was reported as 36% to 47% in studies conducted with the participation of PWID.[13-15]

World Health Organization (WHO) has determined strategies on prevention, screening and treatment of infections caused by HCV and other hepatitis viruses worldwide to reduce the amount of such infections. Improved undiagnosed case detection, wider treatment availability, and improved care coordination are important components of the elimination

strategy. In addition to primary prevention strategies like opioid replacement therapies and needle and syringe programs, early diagnosis and treatment of HCV in PWID, which is considered as high-risk group, will help to reduce complications and mortality related to HCV, especially in PWID. The "treatment as prevention" approach is gaining importance in treatment guidelines, considering the fact that eradication of HCV infection by means of early diagnosis and treatment would impact both individual well-being and reduce the spread of the disease in PWID.[16-20]

PWID has been considered as a difficult patient group to reach, manage and treat because scientific data indicate that the management of the HCV treatment of PWID patient group is challenging and has a higher risk of re-infection. Since direct-acting antiviral (DAA) agents were introduced into treatment guidelines, HCV genotyping has become more important in determining the treatment option which should be given, predicting the probability of responding to the treatment, and determining optimal treatment time. Identification of the HCV genotype is the crucial component for rapid and efficient treatment in difficult patient groups like PWID, given that there are variations among HCV genotypes in terms of geographic distribution, clinical course, and response to treatment.[21-24]

Genetic variability among various HCV genomes has been demonstrated in 7 different main HCV RNA genotypes, which have all been reported so far. HCV genotypes 1a, 1b, and 3a are more common in the general population of countries with higher income levels. However, there are differences in the dominant genotypes between different parts of the world. These differences are linked to clinical traits like migration, geographic distribution, and drug use. While the most frequently observed HCV genotype worldwide is genotype 1 with a rate of 46% to 49%, this is followed by HCV genotype 3, with a rate of 22%.[2,5,25] HCV genotype 1 was found to be more prevalent in Europe and America, HCV genotype 4 in the Middle East and Northern Africa, HCV genotype 5 in Southern Africa, HCV genotype 3 in Southeastern Asia, and HCV genotypes 1a and 3 in Asia. HCV genotype 3 prevalence is increasing in Europe every year, associated with opiate trafficking from India and Afghanistan and migration.[22,24-26]

In research carried out with the general population in Turkey, HCV genotype 1 is detected with a frequency of 76% to 93%, HCV genotype 3 with a rate of 3.7% to 6.7%, HCV genotype 2 with a rate of 1.5% to 2.2%, and HCV genotype 4 with a rate of 1.1% to 9.8%. 80% of HCV genotype 1 cases are HCV genotype 1b.[5,21,27,28] Even though there aren't many studies showing that genotypes vary among PWID in Turkey, HCV genotypes 3 and 1 are the most common, with rates of 58.6% and 50.4% to 61%, respectively.[29-31] This difference in genotypic distribution may be due to common needle sharing within the PWID group, as well as different immunological mechanisms that help the persistence of different genotypes in patients with PWID. Although genotype-specific treatment options are just beginning to take place in health policies in Turkey, it is important to reveal the genotype differences especially in PWID patients.

HCV genotyping gives information about the clinical outcome of HCV infection, recommendations for drug choice based on an individual's needs, response to pharmacological therapies, follow-ups for adverse effects, and the length of therapy. In comparison to other genotypes, genotype 3 infection has been linked to a higher chance of cirrhotic patients developing hepatocellular carcinoma, hepatic steatosis, and rapid hepatic fibrosis progression. Direct-acting antivirals (DAAs), which are therapeutic medicines divided into several classes according on their target and mode of action, have been developed in an effort to eradicate this disease. Patients with HCV genotypes 1 and 4 are less likely to complete their treatment than those with genotypes 3 and 4. Since this patient group's pharmacological intervention is maintained for a longer duration of time, genotypes 1 and 4 have poor treatment compliance. When interventions and treatment are tailored to each person's genotype, therapy adherence will go up and the number of people with HCV will decrease.[32]

The goal of this study was to identify HCV genotype variations and associated factors in PWID across Turkey. We believe that the results of this study will become a source for national treatment guidelines regarding HCV screening, diagnosis, and treatment, as well as for epidemiological studies.

## Method

### *Study design*

This study was designed as a multicenter and prospective study, and its ethical approval was taken from Uskudar University Ethical Board of Clinical Studies (12.04.2018-61351342 /2018/06). The study included 197 patients. They were enduring inpatient and outpatient treatment at the Alcohol and Substance Addiction Treatment Centers (AMATEM) of Akdeniz University Medical Faculty (Akdeniz UMF), Ankara Numune Training and Research Hospital (Ankara NTRH), and Bakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital (Bakirkoy MHNH) between May 2018 and May 2019 due to injecting drug use, and screening revealed that they had anti-HCV antibodies. Male and female patients older than 18 years old were included in the study after they signed the approval form prepared to enroll in the study. The patients with transmission history at birth, and the patients having treatment due to HCV infection were excluded from the study.

After the patients completed the forms with their demographic information and drug use history, blood samples of 10 mL were collected for serological measurements. HCV viral

load and genotyping measurements were conducted with the blood samples collected. Information forms and biological materials were recorded with the patients' initials and the patient number assigned by the treatment centers.

### *Laboratory procedures*

In this study, HbsAg, Anti-HCV antibodies and Anti-HIV tests were performed on Cobas e601 analyzer with ELECSYS (Electrochemiluminescence Immunoassay) method at Duzen laboratories. Elecsys HbsAg 2 kits were used for Hepatitis B surface antigens, and qualitative specification was performed. Elecsys Anti-HCV 2 kits were used for Hepatitis C antibodies, and qualitative specification was performed. Anti-HIV antibodies were analyzed with HIV combi PT kits. This test specifies HIV type 1 p24 antigens and type 1/2 IgG antibodies simultaneously.

HCV RNA was analyzed by means of RT PCR method on Cobas AmpliPrep/CobasTaqman 48 (Roche) system. The linear range of this test is 15 to 100 000 000 IU/mL. HCV GENOTYPE sequence analysis was performed with 2 different methods. The first method was performed on ABI 3130/3130XL device. The screening was performed for genotypes 1, 2, 3, 4, 5, 6, and their subtypes. The second was performed with RealTime method on Montania 4896 system. The screening was performed for genotypes 1, 1a, 1b, 2, 3, 4, 5, 6.

### *Statistics*

Statistical evaluations were conducted by using "SPSS (Statistical Package for Social Sciences) for Windows 20.0" software package. The data and averages and percentage values of the results in the form of tables were used to compare independent groups, and arithmetic averages and standard deviation values were applied for descriptive statistics. Analyses were conducted by means of Mann-Whitney *U* test, Chi-Square, and One-way ANOVA. Error margin was set as $P = .05$. *P*-values equal to or smaller than this value were interpreted as statistically significant for differences. The limit for statistically significant results was set as .95 ($P < .05$).

## Results

### *Demographic information*

The study included 197 individuals with anti-HCV antibodies who were getting outpatient and inpatient care due to injecting drug use at 4 different AMATEMs in Turkey. The main characteristics of the patients are shown in Table 1. HCV genotyping of 61 patients (55 males, 6 females) among 197 patients with anti-HCV antibodies could not be performed because their HCV viral load was inadequate. HCV genotyping of a total of 136 patients consisting of 126 (92.6%) males and 10 (7.4%) females was performed, and the patients' distribution according to the addictions treatment centers is as follows: a total of 70 patients (51.5%) consisting of 65 males and 5 females from Akdeniz UMF, 33 male patients (24.3%) from Bakirkoy MNDH, 18 male patients (13.2%) from Ankara NTRH, and a total of 15 patients (11.0%) consisting of 10 males and 5 female patients from Erenkoy MNDH.

The genetic profiles of the 136 patients were as follows: 46.3% had genotype 1, 44.1% had genotype 3, 5.1% had genotype 2 and 6, 4.4% had genotype 4. 9.5% had genotype 1b, while 90.5% of those with type 1 genotype had genotype 1a. When we evaluated the most frequently observed genotype distribution according to the subtypes, the most frequently observed genotype was genotype 3 with 44.1%, while this was followed by genotype 1a with 41.9%. We did not observe any statistically significant difference among genotype groups regarding the viral loads (Table 1).

The average age of the 136 patients genotyped was $30.3 \pm 8.6$. We did not observe any statistically significant difference regarding the patients' mean age among the genotype groups. Furthermore, we did not observe any statistically significant difference after the analysis of the patients' sociodemographic characteristics, such as education level, marital status, employment status, acceptance type, and criminal record history, with respect to genotype groups (Table 1).

Table 2 shows the assessments of viral parameters for addiction treatment facilities. The mean rate of viremic HCV was 69.03% (136/197) based on the rate of HCV RNA positivity over patients with anti-HCV positivity. We did not observe any statistically significant difference among the viremic HCV load among the addiction treatment centers ($P > .05$).

The distribution of genotypes with respect to addiction treatment centers are shown in Table 2. Among 70 patients with HCV RNA positivity and enrolling the study from Akdeniz UMF, 42.9% were genotype 1a, 42.9% were genotype 3. Among 18 patients with HCV RNA positivity and enrolling the study from Ankara NTRH, 44.4% were genotype 3, 27.8% were genotype 1a, 22.2% were genotype 2. Among 33 patients with HCV RNA positivity and enrolling the study from Bakirkoy MNDH, 48.5% were genotype 3, 45.4% were genotype 1a. Among 15 patients with HCV RNA positivity and enrolling the study from Erenkoy MNDH, 46.7% were genotype 1a, 40.0% were genotype 3. We found a statistically significant difference among patient groups according to the statistical analysis performed ($P = .034$).

## Discussion

In this study, we aimed at identifying HCV genotypes and associated risk factors among patients who had anti-HCV positivity and were receiving treatment from 4 different AMATEM clinics located in various geographical regions of Turkey, that is, the south of Turkey, central Anatolia, and northwest Anatolia, for injecting drug use. Even though there have been a number of studies on HCV genotypes in the general population that show endemic and epidemic

**Table 1.** Sociodemographic characteristics with respect to genotypes.

| | TOTAL | HCV GENOTYPE 1A | HCV GENOTYPE 1B | HCV GENOTYPE 2 | HCV GENOTYPE 3 | HCV GENOTYPE 4 | *P* |
|---|---|---|---|---|---|---|---|
| Frequency, n (%) | 136 (100) | 57 (41.9) | 6 (4.4) | 7 (5.1) | 60 (44.1) | 6 (4.4) | |
| Gender (M/F) | 126/10 | 52/5 | 6/0 | 6/1 | 56/4 | 6/0 | >.05 |
| Age (mean ± SD) | 30.3 ± 8.6 | 30.7 ± 8.0 | 36.8 ± 15.1 | 24.2 ± 5.4 | 30.9 ± 8.7 | 28.5 ± 4.6 | >.05 |
| HCV RNA (IU/mL) | $2.53 \times 10^6$ | $1.54 \times 10^6$ | $2.48 \times 10^6$ | $3.42 \times 10^6$ | $3.4 \times 10^6$ | $1.59 \times 10^6$ | >.05 |
| Education level, n (%) | | | | | | | |
| Primary education/ uneducated | 49 (36.1) | 21 (42.9) | 4 (8.2) | 1 (2.0) | 21 (42.9) | 2 (4.1) | .568 |
| Secondary education | 78 (57.4) | 33 (42.3) | 2 (2.6) | 6 (7.7) | 33 (42.3) | 4 (5.1) | |
| University education | 9 (6.6) | 3 (33.3) | 0 (0) | 0(0) | 6 (66.7) | 0 (0) | |
| Marital status, n (%) | | | | | | | |
| Single | 96 (70.6) | 44 (45.8) | 3 (3.1) | 6 (6.3) | 39 (40.6) | 4 (4.2) | .720 |
| Married | 26 (19.1) | 9 (34.6) | 2 (7.7) | 0 (0) | 13 (50.0) | 2 (7.7) | |
| Divorced | 14 (10.3) | 4(28.0) | 1(7.0) | 1 (7.0) | 8 (56.0) | 0 (0) | |
| Employment, n (%) | | | | | | | |
| Does not have a regular job | 40 (29.4) | 23 (37.1) | 2 (3.2) | 3 (4.8) | 31(50.0) | 3 (4.8) | .489 |
| Has a regular job | 62 (45.6) | 19 (47.5) | 1 (2.5) | 2 (5.0) | 16 (40.0) | 2 (5.0) | |
| Unemployed | 30 (22.1) | 15 (50.0) | 3 (10.0) | 1 (3.3) | 10 (33.3) | 1 (3.3) | |
| Student | 4 (2.9) | 0 (0) | 0(0) | 1 (25.09 | 3 (75.0) | 0 (0) | |
| Patient acceptance type, n (%) | | | | | | | |
| Outpatient | 91 (66.9) | 41 (45.1) | 3 (3.3) | 6 (6.6) | 38 (41.8) | 3 (3.3) | .453 |
| Inpatient | 45 (33.1) | 16 (35.6) | 3 (6.7) | 1 (2.2) | 22 (48.9) | 3 (6.7) | |
| Imprisonment history, n (%) | | | | | | | |
| Exists | 63 (46.3) | 25 (39.7) | 3 (4.8) | 4 (6.3) | 28 (44.4) | 3 (4.8) | .970 |
| None | 73 (53.7) | 32 (43.8) | 3 (4.1) | 3 (4.1) | 32 (43.8) | 3 (4.1) | |

characteristics based on geographic differences, there have been very few studies on how HCV genotypes are spread among PWID. The significance of this study is increased by the fact that we had samples from different geographic areas of Turkey as a result of our multicenter design. The study's findings showed that among 136 PWID with a history at 4 different addiction treatment centers, genotype 3 was the most frequently observed HCV genotype with a rate of 44.1%. This was followed by genotype 1a with a rate of 41.9%, genotype 2 with a rate of 5.1%, genotype 1b with a rate of 4.4%, and genotype 4 with a rate of 4.4%.

Among the patients with anti-HCV positivity, genotype 3 was the most frequent sub-type. Whereas the results of general population studies in Turkey indicated that genotype 1b is the most prevalent sub-type. In addition, the results of other studies involving PWID indicated that genotypes 1a and 3 are the most prevalent, which is consistent with the findings of the present study.[27,29-31] According to studies looking for HCV genotype prevalence worldwide, the rates of genotype 1b are low among PWID, while the rates of genotype 1a, which is dominant, and genotype 3 are gradually increasing over time.[25,33] Similar to the findings of our study, the study conducted by Üçbilek et al[29] in the Cukurova region with 97 PWID indicated that HCV genotype 3 was the dominant type with a rate of 58.6%. However, unlike our study, genotype 1a was found dominant with a rate of 61.1% in another study conducted with the enrollment of 36 young PWID who migrated from the Cukurova region to Istanbul.[31] In another study conducted in Mersin with the participation of 238 PWID, genotype 1a dominance was shown at a rate of 57.1%.[30] In studies conducted in the southern parts of Turkey among PWID, unlike genotype 3 dominance observed in this study, the

**Table 2.** Viral parameters with respect to addiction treatment centers.

| | AKDENIZ UMF, N (%) | ANKARA NUMUNE TRH, N (%) | BAKIRKÖY MNDH, N (%) | ERENKÖY MNDH, N (%) | *P* |
|---|---|---|---|---|---|
| HCV RNA +/Anti-HCV + | 70/109 (64.2) | 18/22 (81.8) | 33/44 (75.0) | 15/22 (68.1) | .308 |
| HCV RNA (IU/mL) | $2.24 \times 10^6$ | $2.79 \times 10^6$ | $2.89 \times 10^6$ | $2.76 \times 10^6$ | .874 |
| Genotype | | | | | .034 |
| 1a | 30 (42.9) | 5 (27.8) | 15 (45.4) | 7 (46.7) | |
| 1b | 4 (5.7) | 0 (0) | 2 (6.1) | 0(0) | |
| 2 | 1(1.4) | 4 (22.2) | 0 (0) | 2 (13.3) | |
| 3 | 30 (42.9) | 8 (44.4) | 16 (48.5) | 6 (40.0) | |
| 4 | 5 (7.1) | 1 (5.6) | 0 (0) | 0 (0) | |

presence of genotype 1a dominance has been attributed to the fact that HCV genotypes indicate changes with respect to geographical characteristics, and this could be associated with sharing needles/syringes among the groups in similar regions. In the study conducted by Suntur et al in the southern regions of Turkey with 869 HCV RNA positive patients, it was indicated that 61.5% were genotype 3, 20.8% were genotype 2, 11.2% were genotype 1a, 5.3% were mixed genotype, 0.6% were genotype 1b, and 0.6% were genotype 4 among 371 PWID. Even though most of the patients in this study who were 40 or older and had any type of disease had genotype 1b, the authors thought that infection through blood transfusion could be the main cause in this patient group, while the fact that genotype 3 was most common in younger patients with substance use disorder showed similarities to our study.[28] It is remarkable that genotype 3 (44.1%) and genotype 1a (41.95%), the 2 most common types in this study, are similarly the 2 most common subtypes in the studies conducted in Turkey until now. It is also remarkable that the dominant type varies with respect to geographical regions. Although there are similarities with respect to genotypes among the addiction treatment centers participating in the multicenter current study, in which HCV genotype 3 is generally more prevalently observed among PWID, the genotyping results of Akdeniz UMF and Erenkoy MNDH centers indicate some differences. Our study indicated that genotype 3 was dominant at Bakirkoy MNDH and Ankara NTRH, genotype 1a was dominant with a rate of 46.7% similar to the study of Yetim and Kandemir at Erenkoy MNDH, and genotype 1a and genotype 3 had an equal distribution among 70 patients enrolling from Akdeniz University representing Cukurova region in southern Turkey. Even though this study couldn't find out why genotypes showed regional differences among PWID, it is said that factors like the way the virus spreads, transnational drug trafficking, and transnational migration could have an effect on the different topics studied in global studies on genotype differences and how they are spread.[22,34,35] Finding genotype differences among addiction treatment facilities revealed that the treatment method of the patients should be changed and hepatitis C virus should be handled differently.

The proportion of patients with anti-HCV antibodies to those who tested positive for HCV RNA was 136/197, or 69.03%, making this study's viremic HCV rate. This is comparable to the global viremia rates,[2] which were discovered to be 67%.

The study's limitations include the difference in patient populations between addiction treatment facilities, the lower proportion of female patients compared to male patients, and the lack of evaluation of available treatments for the genotypes that were identified.

## Conclusion and Recommendations

Since HCV infection prevalence rates are higher in PWID, identifying HCV RNA genotypes in cases of anti-HCV antibodies positivity may aid in determining clinical prognosis, treatment responses, and other aspects for the subject patient groups. Antiviral medication therapies that are initiated in accordance with an individual's HCV genotype have been found to lower HCV infection rates in at-risk groups by weakening the infection and the virus. PWID and members of the general population have distinct genotypes. Different countries and regions within a country have different HCV genotypes because of a number of factors, mostly related to geography and economics. When PWID share needles and syringes, people in the same group are more likely to have the same genotype. We believe that revealing the genotype differences among study centers will be beneficial for better understanding of the spread of viral infections and taking necessary measures. More comprehensive studies with wider samples are required with respect to reasons for observing different genotypes observed in different geographical regions of Turkey. Identification of genotypes will be useful in developing individualized treatments and determining national prevention strategies.

Raising public awareness of infectious diseases, screening high-risk patient populations for infectious diseases, and

establishing national healthcare regulations that allow patients access to and maintenance of treatment are all critical among PWID. Due to the challenges associated with putting harm-reduction initiatives like maintenance treatments and the provision of safe needles and syringes into practice, we believe that prompt diagnosis and treatment of infectious diseases will contribute to reducing the spread of infections among at-risk groups.

## Acknowledgements

We extend our thanks to all participating investigators.

## Author Contributions

Concept: Nesrin Dilbaz. Design: Nesrin Dilbaz. Data Collection and/or Processing: Nesrin Dilbaz, Murat Kuloğlu, Ekrem Cüneyt Evren, Salih Cihat Paltun, Rabia Bilici, Cemal Onur Noyan, Burak Kulaksızoğlu, Vahap Karabulut, Gökhan Umut, Başak Ünübol. Analysis and/or Interpretation: Nesrin Dilbaz. Literature Search: Nesrin Dilbaz. Writing Manuscript: Nesrin Dilbaz.

## Ethics Committee Approval

İnstitution name: Üsküdar University Clinical Research Ethics Committee, Istanbul, Turkey. Approval number: Decision no.: 2018/04 - Decision date: 11.04.2018. The date it was received and number: 12.04.2018 and 61351342/2018/06. The study was conducted in accordance with the principles of the current revision of the Declaration of Helsinki and Good Clinical Practice procedures and approved by the Human Research Ethics Committee of Üsküdar University.

## Informed Consent

Signed consent forms were obtained from all patients included in the study, stating that they voluntarily agreed to participate in the study.

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