



Hepatitis C Coinfection Among People Living with HIV in a University Hospital in İstanbul

İstanbul'da Bir Üniversite Hastanesinde HIV ile Yaşayan Bireylerde Hepatit C Koenfeksiyonu

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ABSTRACT

Objectives: Human immunodeficiency virus (HIV) has infected millions of people throughout the world and may co-exist with other infections due to common ways of transmission. In our study, we aim to assess the prevalence of hepatitis C virus (HCV) coinfection among people living with HIV (PLWH) as well as infection transmission ways, treatment responses of the treated patients.

Materials and Methods: Five hundred thirty PLWH were included in the study, monitored in our clinic between 2014 and 2020. Age, gender, education level, date of diagnosis and follow-up period, transmission ways, clinical observations and anti-HCV data of patients were retrospectively analyzed.

Results: Of the subjects 92.3% (n=489) were males, and 7.7% (n=41) were females. 1.7% (n=9) of patients were detected with anti-HCV positivity. 0.6% (n=3) of the anti-HIV positive patients had active hepatitis C infection. Anti-HCV positivity was found to be 65 times higher in injecting drug users.

Conclusion: There is no vaccine or post-exposure prophylaxis to protect against HCV. Therefore, HCV has to be monitored in follow-up visits for PLWH, risk factors should be identified, and the patients should be raised awareness of transmission and protection ways. Immediately started antiviral treatment when diagnosed with HCV. Antiviral therapy should be immediately started when HCV is diagnosed.

Keywords: HCV, HIV, coinfection

ÖZ

Amaç: Dünyada milyonlarca insanı etkileyen insan bağışıklık yetmezlik virüsü (HIV), ortak bulaş yolları nedeniyle başka enfeksiyon etkenleri ile birlikte olabilir. Çalışmamızda HIV ile yaşayan bireylerde hepatit C virüsü (HCV) koenfeksiyon sıklığını, bulaş yollarını ve tedavi almış hastalarda tedavi cevabını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: 2014-2020 yılları arasında kliniğimizde takip edilen 530 HIV ile yaşayan birey çalışmaya alındı. Hastalara ait yaş, cinsiyet, eğitim düzeyi, tanı tarihi ve takip süresi, bulaşma yolları, klinik izlemleri ile anti-HCV verileri retrospektif olarak incelendi.

Bulgular: Olguların %92,3 (n=489) erkek, %7,7 (n=41) kadın idi. Hastaların %1,7'sinde (n=9) anti-HCV pozitifliği saptandı. Anti-HCV pozitif hastaların %0,6'sında (n=3) aktif hepatit C enfeksiyonu mevcuttu. Damar içi madde kullananlarda anti HCV pozitifliği 65 kat daha yüksek bulundu.

Sonuç: HCV'ye karşı koruma sağlayacak bir aşı veya temas sonrası profilaksi yoktur. Bu nedenle, HIV ile enfekte bireylerin takiplerinde HCV izlenmeli, risk faktörleri belirlenmeli, hastalar bulaş ve korunma yolları konusunda bilinçlendirilmelidir. HCV teşhisi konduğunda hemen antiviral tedaviye başlanmalıdır.

Anahtar Kelimeler: HCV, HIV, koenfeksiyon

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Introduction

In Turkey, there are 25,809 people living with HIV (PLWH) verified as of November 2020 (1). These people face several coinfections due to common transmission ways, including viral hepatitis B and C. Hepatitis C virus (HCV) main difference from hepatitis B is that it has no vaccine or post-exposure prophylaxis. In particular the individuals who have shared a contaminated needle and injection, and who made unprotected sexual intercourse are invariably at risk. With highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV)-based opportunistic infections were decreased, and life expectancy prolongation and higher quality of life were increased, whereas morbidities and mortalities second to such infections—secondary to such infections as viral hepatitis C have remained critical (2). Several studies have reported that progression of liver disease is three times more likely in people with HIV/HCV coinfection-coinfection (3).

In our study, we aim to assess hepatitis C prevalence among PLWH we have followed up in our clinic, transmission ways and treatment responses of the treated patients.

Materials and Methods

Five hundred thirty PLWH were included in the study, followed up in Infectious Diseases and Clinical Microbiology at İstanbul Medeniyet University, Göztepe Training and Research Hospital, from January 2014 to September 2020. The data from patient files and electronic records were retrospectively reviewed, including the demographic information, HCV prevalences, transmission ways, treatment information, treatment results and clinical observations of the patients. ELISA was used for anti HCV serology, and polymerase chain reaction for HIV RNA.

Our study was approved by the Ethics Committee of İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2020/0457). All participants were informed about the study before it was conducted and their verbal consents were obtained.

Statistical Analysis

Number Cruncher Statistical System (Kaysville, Utah, USA) was used for statistical analyses. The data were—the data were reviewed using descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum and maximum). Kolmogorov-Smirnov and Shapiro-Wilk tested normal distribution of quantitative data as well as graphical evaluations. For paired comparisons of the normally distributed quantitative data Student's t-test was used, and Mann-Whitney U test for paired comparisons of the non-normally distributed data was used. Pearson chi-square test, Fisher-Freeman-Halton exact test and Fisher's exact test were used for qualitative data. Significance level was defined as $p < 0.05$.

Results

Between January 2014 and September 2020, 530 PLWH was studied; 92.3% ($n=489$) were males, and 7.7% ($n=41$) females. The median age of the patients was 37 (18 to 88), and the median length of follow-up was 4 years (0 to 6). 67.5% ($n=330$) of the patients were men who had sex with other men (MSM). The

most prevalent way of HIV infection transmission was sexual intercourse; 62.3% ($n=330$) was homosexual, 31.7% ($n=168$) was heterosexual. Injecting drug use was detected for 1.3% ($n=7$). The distribution of descriptive characteristics of HIV-infected patients is shown in Table 1.

Anti-HCV positive was found in 1.7% ($n=9$) of the patients. The median age of the cases was 36 years (29 to 68), and the median length of follow-up was 4 years (0 to 5). Of these cases, 44.4% ($n=4$) were female, 55.6% ($n=5$) males. Injecting drug user (IDU) was at 33.3% ($n=3$).

Anti-HCV positive rates had no statistically significant difference depending on anti-HCV positivity rate was not statistically different according to mean ages, age groups, date of diagnosis, education level, length of follow-up, transmission way, being MSM, and CD4 T-lymphocyte count ($p > 0.05$).

A statistically significant difference was found in anti HCV positive rates by gender ($p=0.003$; $p < 0.01$). HCV positivity was found to be significantly higher in women. Anti-HCV was positive in four female patients. One of these patients had a history of operation and multiple blood transfusions, one had a history of injecting drug use.

For IDU, there were statistically significant difference in anti-HCV positive rates ($p=0.001$; $p < 0.01$); IDU had significantly higher anti-HCV positive rate. The ODDS rate was found to be 64.62 (95% confidence interval: 11.81-353.6).

In Table 2, data of HIV patients were compared to those of HIV/HCV coinfecting patients. In Table 2, data of HIV infected patients with and without HCV coinfection were compared. Of anti-HIV positive patients, 0.6% ($n=3$) had HCV-RNA positive. All of HCV-RNA positive patients were examined and all of them were genotype 3. Two of the patients were males and both were MSM and IDU. One of these patients was a Turkish citizen living abroad, who was found to have acute HCV infection and comorbid HIV infection. One patient was a female patient of foreign nationality and had a history of operation and multiple blood transfusions.

A patient used pegylated interferon alpha (Peg-IFN) plus ribavirin, and sustained one patient used Peg-IFN plus ribavirin, and had sustained virological response (SVR). Since the foreign patient did not have social security, she could not receive HCV treatment. Each patients continued to regularly use HAART. Cirrhosis and hepatocellular carcinoma were not observed in the patients during follow-up.

Discussion

The 2017 global hepatitis report of World Health Organization estimated that out of 71 million acute hepatitis C infected people throughout the world, 2.3 million were also HIV-coinfecting (4).

Infection of HCV infection, like HIV, occurs vertically from the mother to the fetus and due to blood and blood components, sexual intercourse and injecting drug use. HIV HCV coinfection rates vary by country. It has been reported the coinfection rates were 12.16% in China (5), 25.6% in Bulgaria (6), 1% in Chile (7), 16.1% in the U.S. (8), and 13.8% in Greece (9), varying by geographical region, age group, risk group, and infection way. In addition, different studies from one country have showed that there were very significant differences depending on risk group. In Brasil, for example, a literature review reported that the rate was

Table 1. Distribution of descriptive characteristics of PLWH

		n	%	
Age (years)	Min-max (median)	-	-	18-88 (37)
	Mean $\pm$ SD	-	-	39.34 $\pm$ 12.03
	<35 years	216	40.8	-
	35-44 years	174	32.8	-
	45-54 years	74	14.0	-
	55-64 years	40	7.5	-
	$\geq$ 65 years	26	4.9	-
Gender	Males	489	92.3	-
	Females	41	7.7	-
Length of follow-up (years)	Min-max (median)	-	-	0-6 (4)
	Mean $\pm$ SD	-	-	3.69 $\pm$ 1.82
Education level	Primary school	27	5.1	-
	High school	39	7.4	-
	College	170	32.1	-
	Unknown	294	55.5	-
MSM (n=489 men)	MSM (-)	127	26.0	-
	MSM (+)	330	67.5	-
	Unknown	32	6.5	-
Transmission way	Heterosexual intercourse	168	31.7	-
	Homosexual intercourse	330	62.3	-
	Unknown	32	6.0	-
Injecting drug use	None	523	98.7	-
	IDU	7	1.3	-
CD4 count cell/mm ³	Min-max (median)	-	-	0-4731 (389)
	Mean $\pm$ SD	-	-	430.75 $\pm$ 327.71
HIV-RNA IU/mL	Min-max (median)	-	-	2-100000000 (198500)
	Mean $\pm$ SD	-	-	3882043.9 $\pm$ 46506767.5
Anti-HCV	Negative	521	98.3	-
	Positive	9	1.7	-
HCV-RNA (n=9)	Negative	6	66.7	-
	Positive	3	33.3	-

PLWH: People living with HIV, min: Minimum, max: Maximum, SD: Standard deviation, MSM: Men who had sex with other men, HIV: Human immunodeficiency virus, HCV: Hepatitis C virus, IDU: Injecting drug user

between 3.3% and 82.4% (10). For Turkey that rate has been found to remain between 0% and 19% (11,12,13,14,15,16,17,18,19). Furthermore, the current study reports that HCV prevalence is 1.7%, and active HCV infection 0.6%, similar to many previous studies conducted in Turkey.

In literature, it has been reported that HCV infection via heterosexual intercourse was rare (20). In a study, Vandelli et al. (21) studied 895 heterosexual monogamous pairs and found that HCV infection risk via sexual intercourse was little if any. Homosexual sexual intercourse has become one of the significant risk factors (22,23). The reason for the high level might be because of a false sense of security due to the HAART use and non-protected traumatized sexual intercourse. In our study, 33.3% (n=3) of the anti-HCV positive patients were MSM. One of these patients

presented with hepatitis, nausea and vomiting and diagnosed with acute hepatitis C infection. The diagnosis of HIV was also made incidentally at the time of the acute HCV diagnosis.

In developed countries, injecting drug use is the key infection route of HCV (24). In a wide range of 4,306 HIV-infected patients, it has been reported that 25.1% of the patients had history of injecting drug use and were detected with HCV-positive in 78.5% of these patients. In Turkey, injecting drug use is not at the top of the list of HCV infection factors. It should be kept in mind that patients may make incomplete or false statements due to the fact that injecting drug use is illegal. In the current study, we showed that injecting drug use increases anti-HCV positive by 65 times. Sharing of syringes, injection applications under non-sterile conditions, unprotected sexual intercourse under the influence of

Table 2. Comparison of HIV patients and HIV/HCV coinfectd patients Comparison of HIV infected patients with and without HCV coinfection

		Anti-HCV		p
		Negative (n=521)	Positive (n=9)	
		n (%)	n (%)	
Age (years)	Min-max (median)	18-881 (40)	29-68 (36)	^a 0.475
	Mean $\pm$ SD	42.73 $\pm$ 13.35	45.18 $\pm$ 12.62	
Age groups	<35 years	214 (41.1)	2 (22.2)	^b 0.406
	35-44 years	170 (32.6)	4 (44.4)	
	45-54 years	72 (13.8)	2 (22.2)	
	55-64 years	40 (7.7)	0 (0)	
	$\geq$ 65 years	25 (4.8)	1 (11.1)	
Gender	Males	484 (92.9)	5 (55.6)	^c 0.003**
	Females	37 (7.1)	4 (44.4)	
Length of follow-up (years)	Min-max (median)	0-6 (4)	0-5 (4)	^d 0.489
	Mean $\pm$ SD	3.69 $\pm$ 1.83	3.33 $\pm$ 1.80	
Education level (n=236)	Primary school	26 (11.1)	1 (50)	^b 0.248
	High school	39 (16.7)	0 (0)	
	College	169 (72.2)	1 (50)	
MSM (n=457)	MSM (-)	125 (27.7)	2 (40.0)	^c 0.621
	MSM (+)	327 (72.3)	3 (60.0)	
Transmission way (n=498)	Heterosexual intercourse	162 (33.1)	6 (66.7)	^e 0.067
	Homosexual intercourse	327 (66.9)	3 (33.3)	
Injecting drug use	None	517 (99.2)	6 (66.7)	^c 0.001**
	IDU	4 (0.8)	3 (33.3)	
CD4 count cell/mm ³	Min-max (median)	0-4731 (388)	3-607 (410)	^d 0.550
	Mean $\pm$ SD	432.16 $\pm$ 329.04	340.12 $\pm$ 221.29	

^aStudent's t-test, ^bFisher-Freeman-Halton exact test, ^cFisher's exact Test, ^dMann-Whitney U Test, ^ePearson chi-square test, *p<0.05, **p<0.01, HIV: Human immunodeficiency virus, HCV: Hepatitis C virus, min: Minimum, max: Maximum, SD: Standard deviation, MSM: Men who had sex with other men, IDU: Injecting drug user

the substance may be the reason for this. It seems that patients with a history of injecting drug use should be evaluated in terms of HIV and HCV infection.

Anti-HCV positivity was found to be significantly higher in women in our study (n=4/41). Three patients were foreigners who were in Turkey for work. All of these patients stated that HIV transmission has happened sexually. Both HCV and HIV can be sexually transmitted. However, it should be kept in mind that some patients have a history such as surgery, multiple blood transfusions and may be transmitted by these ways.

Part of the HCV infected people spontaneously go through the disease while chronic infection develops in 75% to 85% of these patients. While some of the people infected with HCV have the disease spontaneously resolve, chronic infection develops in 75-85% of them. They could either remain asymptomatic or still have risks of cirrhosis, end-stage liver failure, and HCC progression. Studies have shown that gender, age, ethnicity, symptomatic acute infection and whether or not hepatitis B co-infection affect spontaneous HCV recovery, while HIV co-infection is one of the reasons that increase chronicity (25,26).

HIV-related guidelines, national or international, recommend that anti-HCV screening should be made for all HIV-positive

individuals and continued if there are ongoing risk factors such as MSM, injection drug use and when HCV positive is detected the treatment should start. In the beginning of the therapy, due to HCV, drug interactions should be well considered in order to avoid hepatotoxic antiretroviral drug use. If viremia is detected by performing HCV RNA analysis, HCV genotype determination should be made in anti HCV positive patients. In follow-up of seronegative patients, HCV RNA should checked when unexplained elevation of liver enzyme is detected (27).

Also for the patients diagnosed with HCV infection, anti-HIV test should be required due to common transmission ways. In this study, HIV diagnosis of a patient was detected during his hospitalization due to acute hepatitis C infection.

Therefore, anti-HIV tests should be regularly performed for HCV positive patients having risky behaviors, and anti-HCV tests for HIV positive ones.

HIV/HCV coinfectd people are more likely to have fibrosis, cirrhosis and related complications than only HCV positive ones, and thus early diagnosis and treatment become crucial (26,28,29). In a study including 1,176 anti-HCV positive patients in America, 34% of who were coinfectd, it was observed that fibrosis stages of coinfectd patients were similar to those of HIV negative

individuals 10 years older (30). In another study in which 23,441 HIV infected patient were monitored, it was found that 66.1% of 181 liver-related deaths had HCV positivity (31). In a cohort study performed in Sweden, it was showed that active HCV infection was present in 45% of deaths (32). In the present study, we observed that no patients developed cirrhosis during follow-up controls. We believe that for the HIV diagnosed patients at a young age, early detection of HCV positivity and immediate start to antiviral treatment can prevent progression of complications.

Anti-HCV positivity does not always prove the presence of active hepatitis C infection. Therefore, HCV-RNA should be considered, whether the individual have viremia or not. In this study, we found active infection in 3 of 9 patients were detected with anti-HCV positive. We could not start treatment two patients. We could not start treatment to two patients. A patient returned-one patient returned to his home country. One patient detected with HCV positivity was planned to administer direct-acting antiviral agents, however, the patient could not receive the treatment because she did not have social security. As a treatment, Peg-IFN and ribavirin was administered to one patient for 24 weeks, and HCV-RNA negativity was observed even in post-treatment follow-up at the 6th month and the patients had the SVR. It was thought that the high level of SVR in our patients high level of SVR in our patient which was defined as the level of HCV-RNA that could not be measured 6 months after the end of treatment, was due to reasons such as good adherence, young age and being Caucasian.

HCV seroprevalence was not found very high in our center and it is similar to other studies conducted in our country. One of the key factors of such low prevalence was lower frequency of injection drug use. The majority of the HIV-positive population being in the young age group, as well as early diagnosis of HCV and HIV and early initiation of treatment prevent possible complications.

Study Limitations

The limitation of the study is that it is a retrospective study, so all patient datas all patient's data were not available

Conclusion

PLWH are at risk due to HCV without vaccine and post-exposure prophylaxis. PLWH are at risk of HCV infection since there is no vaccine and postexposure prophylaxis. Patients should be made aware of transmission ways, regularly screened, and immediately started antiviral treatment when diagnosed with HCV.

Ethics

Ethics Committee Approval: Our study was approved by the Ethics Committee of Istanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2020/0457).

Informed Consent: All participants were informed about the study before it was conducted and their verbal consents were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.E., Desing: P.E., H.Ç., Data Collection or Processing: P.E., Analysis or Interpretation: P.E., H.Ç., Literature Search: H.Ç., Writing: P.E., H.Ç.

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