

Hepatitis E virus seroprevalence in HIV positive individuals in Shiraz, Southern Iran

Hassan Joulaei¹, Omid Rudgari¹, Nasrin Motazedian^{1*}, Samaneh Gorji-Makhsous²

¹Shiraz HIV/AIDS Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

²Health Policy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Received: December 2014, Accepted: February 2015

ABSTRACT

Background and Objectives: Hepatitis E virus (*HEV*) is the most common cause of acute viral hepatitis in the world. It is usually a self-limited disease but may lead to the deaths of about 20% of pregnant women in developing countries. This study was conducted to determine the prevalence of *HEV* infection among *HIV* individuals.

Materials and Methods: This is a cross-sectional survey of *HIV* positive individuals in voluntary counselling and testing center of Shiraz in 2013. Using the systematic random sampling method, 158 patients enrolled for the research. They were asked about their age, gender, area of residence, marital status, number of children, education level, occupation, history of imprisonment, mode of *HIV* transmission, and viral hepatitis co-infection. Three ml venous blood sample was drawn from each subject and transferred to the laboratory of voluntary counselling and testing center.

Results: The overall seroprevalence of hepatitis E was 26 (16.4%), where it increased significantly with age ranging from zero in subjects less than 30 years of age to 47.4% in those aged 50 years or older.

Conclusion: Co-infection of *HIV* positive individuals with *HEV* is an issue that should be of concern to health care providers.

Keywords: Hepatitis E, HIV, Seroprevalence.

INTRODUCTION

Worldwide 20 million hepatitis E infections, more than three million acute cases of hepatitis E, and 57000 hepatitis E-related deaths occur every year. Hepatitis E can be found globally, but the highest prevalence in the world is found in the East and

South of Asia. As a whole, Hepatitis E virus (*HEV*) is the most common cause of acute viral hepatitis in the world. It is also endemic in many developing countries. Hepatitis E is usually a self-limited disease but it leads to the deaths of about 20% of pregnant women in developing countries (1, 2).

A study reported *HEV* seroprevalence as 2.6% among *HIV*-infected patients with liver enzyme elevation (3). Another study conducted on *HIV* positive pregnant women, 6.6% had IgG antibodies to *HEV* (4).

Iran is located in south of Asia, and had experienced few suspected outbreaks of *HEV*. The epidemics of *HEV* infection in this country have been reported from Kermanshah (west of Iran), Isfahan (center of Iran), and Lordegan (Southwest of Iran) (5). Studies among blood donors in Iran have shown

*Corresponding author: NasrinMotazedian, MD.
Address: Shiraz HIV/AIDS Research Center, Shiraz University of Medical Sciences, 2nd floor, Voluntary Counseling and Testing Center, Lavan Ave, Delavaran-e-BasijBlvd, KhatounSq, Shiraz, Fars, Iran.
Post Code: 71659-83885
Tel: +98-711-7386272
Fax: +98-711-7386272
E-mail: motazediann@yahoo.com

that the prevalence of HEV infection is 4.5% in Tehran (6), 7.8% in Tabriz (7), and 11.5% in Khuzestan (8).

Population based studies in Iran showed that Anti-HEV antibodies were detected by 2.3% in Sari district (9), 7.8% in Western Iran (10), 9.3% in the city of Nahavand (11), and 3.8% in Isfahan (12). The population based studies showed the high percentages of HEV infection prevalence belongs to Mashhad (14.2%) (13) and Arak (14.3%) (14).

A study conducted in Urmia showed only five (3.6%) cases among 136 pregnant women had anti-HEV IgG positive (15).

HEV can lead to acute hepatitis, but reports have shown on chronic hepatitis in organ transplant recipients, and reactivations of HEV after stem cell transplantation. Evidence of acute HEV infections and persistent carriage of HEV have been reported in HIV-positive patients (16).

Among HIV-infected patients in Tehran, 10% had antibodies to hepatitis E virus; this result was not significantly different from uninfected controls (11.5%) (17).

To the best of our knowledge, most studies conducted on the prevalence of HEV were among blood donors or general population in Iran. There are only few reports regarding incidence of HEV among HIV positive individuals in Iran. The present study was then conducted to determine the prevalence of HEV infection among HIV individuals in Shiraz, southern Iran.

MATERIALS AND METHODS

Study population. This study comprised a cross-sectional survey of HIV positive individuals attending the voluntary counseling and testing (VCT) center in Shiraz for a period of one year (2012-2013). HIV positive individuals aged over 18 years which, referred to the center for routine visit were asked to participate in our study. Using the systematic random sampling method, 158 patients enrolled for the research. The study started after the subjects were informed about the study and provided written informed consent to participate in the program.

A data collecting form was designed which contained information regarding subject age, gender, area of residence, marital status, number of children, education level, occupation, history of imprison-

ment, mode of HIV transmission, and viral hepatitis co-infection.

Laboratory procedures. Three ml venous blood sample was drawn from each subject and transferred to the laboratory of VCT. The blood sample obtained was centrifuged at 3000 rpm for 10 min to separate serum, which was then stored at -20°C until used for anti-HEV antibody assay. The presence of anti-HEV in human sera was determined using a commercial HEV ELISA kit (Dia-pro, Milan, Italy) according to the manufacturer's instructions.

Statistical Methods. The collected data were coded, analyzed, and computed using the Statistical Package for Social Sciences (SPSS) version 18. Descriptive statistics and Chi-square tests were used in the statistical analysis and a P-value of <0.05 was considered significant. Our study was approved by the Ethics Committee of Shiraz University of Medical Sciences.

RESULTS

The mean age of 158 HIV-infected patients was 39.1 (SD = 8) years. The study comprised 112 men (70.9%) and 46 women (29.1%). The reported routes of HIV transmission were intravenous drug use (IDU) alone in 27 (17.1%), only sexual contact in 52 (32.9%), sexual contact and IDU in 67 (42.1%), and infected blood in 3 (1.9%) subjects. The transmission route of HIV in 9 (5.7%) of patients was unknown. The overall seroprevalence of hepatitis E was 26 (16.4%), which had a positive correlation ($P < 0.001$) with age ranging from zero in subjects less than 30 years of age to 47.4% in those aged 50 years or older (Table 1).

There were no significant association between gender, marital status, number of children, and education level, occupation, history of imprisonment, mode of HIV transmission, and HEV seropositivity among our participants.

The prevalence of infections, in our HIV suffering participants was 76 (75.2%) for HCV, 5 (5%) for HBV, and 2 (2%) for tuberculosis infection (TB). The prevalence of co-infections among HEV positive individual were, 70.6% (n=12) for HEV/HCV, 5.9% (n=1) for HEV/TB, 5.9% (n=1) for HEV/HCV/TB, and 5.9% (n=1) for HEV/HBV/HCV/TB. Characterist-

ics of our participants are shown in Table 2.

Table 1. The prevalence of anti-HEV according to age among HIV positive individuals in Shiraz, Iran in 2013

Age(years)	Anti-HEV positive n (%)	Anti-HEV negative n (%)	Total n (%)
0-29	0(0)	12(100)	12(100)
30-49	17(13.4)	110(86.6)	127(100)
>=50	9(47.4)	10(52.6)	19(100)
total	26(16.5)	132(83.5)	158(100)

Table 2. The characteristics of 158 participants according to result of HEV test in Shiraz, Iran 2013

Variables	Anti-HEV patients N=26	positive Anti-HEV patients N=132	negative P- value
Age	44.9± 9.3 ^a	37.4± 7.3 ^a	0.001
Sex			
Men	20(76.9)	92(69.7)	0.458
Women	6(23.1)	40(30.3)	
Marital status			
Single	3(11.5)	37(28.2)	0.203
Married	17(65.4)	69(52.7)	
Others	6(23.1)	25(19.1)	
Occupation			
Permanent job	6(23.1)	24(19)	0.541
Temporary job	18(69.2)	82(65.1)	
Unemployed	2(7.7)	20(15.9)	
Education			
None	2(7.7)	5(3.8)	0.814
1-5 years	9(34.6)	43(32.6)	
6-9 years	9(34.6)	53(40.2)	
More than 10 years	6(23.1)	31(23.5)	
Mode of HIV transmission			
IDU	5(19.2)	22(16.7)	0.203
Sexual transmission	9(34.6)	43(32.6)	
IDU & sexual transmission & Other	12(46.2)	67(50.8)	
Number of children			
1	7(33.3)	38(52.1)	0.122
2	6(28.6)	22(30.1)	
>=3	8(38.1)	13(17.6)	
Imprisonment			
Yes	17(65.4)	78(59.1)	0.549
No	9(34.6)	54(40.9)	

a: Mean±SD .

DISCUSSION

Susceptibility of HIV positive individuals to HEV is a controversial issue. The result of investigations from endemic parts of the world showed higher HEV seroprevalence rates in HIV-infected individuals and also its association with late stage of HIV infection. It is not clear if this is due to an opportunistic infection or common method of transmission (18). Risk of acquiring HEV could be explained as anal sexual contact among HIV positive individuals which may also account for other enteric infections (e.g., Giardia). However, this association is dismissed by other researchers.

We found no significant difference in HEV seropositivity between subjects regarding gender, possible modes of HIV transmission, education, number of children, profession, marital status, and history of imprisonment. Furthermore, as shown in Table 1, the seroprevalence of HEV increased significantly with growing age. Therefore, a higher prevalence of anti-HEV positivity was observed among individuals aged 50 years and older.

Our study indicates higher prevalence of HEV/HIV co-infection in our region than reports from southwest of England (2), Tehran (17), Switzerland (3) and central Africa (4). The seroprevalence of HEV among HIV infected patients in our study was higher than epidemiological studies of general populations of Iran; Sari district (9), Western Iran (10), Nahavand (11), and Isfahan (12). The population based studies showed the higher prevalence of HEV infection (14.2%) in Mashhad (13) and 14.3% in Central Province (14). Other studies from southwest of England (2) and Tehran (17) found no difference in anti-HEV seroprevalence between HIV infected patients and controls group (HIV negative persons).

Recently a study from Spain in 2014 was found anti-HEV IgG antibodies in 10.4% of patients infected with HIV. The survey compared its result with other studies in the same geographic area. The prevalence was higher than other groups such as; blood donors, hemodialysis patients, pregnant women, and other considered high risk groups (except pig handlers (19)). Although a study from Russia found opposite result; the seroprevalence of HEV among blood donors was more than HIV individuals. Sharipova *et al.*, claim that lower frequency of HEV detection among HIV patients could attribute to interplay of viruses in case of HIV/HEV co infection (20).

We note that our finding in HEV seroprevalence was higher in adult HIV patients from Ghana (45.3 %) than our study (21). A study from Spain also reported higher prevalence of co-infection (26%) than our study (22), as did another study conducted from NIH HIV-Transplant Cohort showed overall prevalence of anti-HEV IgG approached 20% among those with HIV and awaiting solid organ transplantation (23).

Recently, a retrospective study in America reported HEV as a possible cause of liver abnormalities in HIV-infected patients. HEV is currently considered new cause of acute hepatitis in HIV-infected individuals (24). Mamun-Al-Mahtab *et al.*, reported HEV infection leading to wide spectrum of liver diseases in Bangladesh, ranging from severe acute viral hepatitis, fulminate hepatic failure, to decompensating cirrhotic liver (25).

Reports suggest that HEV can lead to chronic infection also evidenced in immunosuppressed HIV patients with chronically elevated liver enzymes (26). Recent reports from India and Europe showed that HEV could exacerbate pre-existing chronic viral hepatitis, leading to poor prognosis in patients with chronic liver disease. This issue might be significant in HIV-infected patients with high rates of chronic co-infections with hepatitis B or C viruses, especially in those with a history of injecting drug use (27). On the other hand the results of a cohort study in England claimed no incidence of chronic HEV/HIV co-infection in group of 138 HIV infected patients (2). A review article in 2015 stated that chronic co-infection of HIV-HEV is not prevalent. Chronic infection was found in patient with CD4<250 cells/ μ L (28).

HEV co-infection should be considered in case of HIV infected patients presenting with abnormal liver function test of unclear etiology (24). Therefore clinical work up of HIV-infected individuals with acute hepatitis should include HEV RNA testing to ensure definite diagnosis of hepatitis E. The negative result should be monitored until complete recovery from infection is confirmed (27).

Alavian *et al.*, underline that HEV should be considered in any viral hepatitis without evidence of HAV and HBV infection in Iran. Contamination of water supplies with sewage is the main cause of outbreak and occurs more commonly along western and eastern borders of Iran, which call for serious attention of health providers. History of recent jour-

ney to Iraq, Pakistan, and Afghanistan in any patient with symptoms of acute viral hepatitis should raise suspicion of HEV infection. People travelling to these countries should be cautioned by Health care providers regarding modes of HEV transmission. HEV might link to serious clinical problems in HIV-seropositive individuals (3). Therefore, providing clean drinking water, improving the sanitary infrastructure could prevent HEV infection in our region.

Increase in HEV seropositivity among HIV infected individuals is not approved in all studies. Ramezani *et al*, (3) and Kuniholm *et al*, (24) reported HIV-infected individuals are not at increased risk of acquiring HEV infection, compared to general population.

Liver injury by antiviral medication leads to uncertainty in the diagnosis of HEV/HIV co-infection especially if serological tests are unreliable. This highlights the importance of PCR for HEV RNA-detection (29). Chronic liver disease deteriorated by HEV, can be differentiated from drug-induced liver injury, HBsAg carrier state, or positive HCV RNA test (16).

Nonetheless, co-infection of HIV positive individuals with HEV is an issue of concern to health care providers. HIV positive individuals with abnormal liver function test should be in differentiated diagnosis of co infection HIV-HEV.

It may also be possible that divergent results observed in our study are due to different study modalities, nutritional, and social habits, sanitary conditions and geographical characteristics of region under the study, and antibodies detection test may play a role in explaining these differences. Therefore, the seroprevalence of anti-HEV IgG among HIV infected individuals differ in different counties.

Currently there is no study regarding prevalence of HEV in general population of Shiraz. Therefore, we could not compare prevalence of HEV infection in HIV infected patients and HEV infection in healthy population of this province. A population based study in Shiraz recommended.

REFERENCES

1. Fact sheet N°280, Updated July 2013, Hepatitis E. Available from: <http://www.who.int/mediacentre/factsheets/fs280/en/>
2. Keane F, Gompels M, Bendall R, Drayton R, Jennings L, Black J, et al. Hepatitis E virus coinfection in patients with HIV infection. *HIV Med* 2012; 13(1):83-8
3. Kenfak-Foguena A, Schöni-Affolter F, Bürgisser P, Witteck A, Darling KE, Kovari H, et al. Hepatitis E Virus seroprevalence and chronic infections in patients with HIV, Switzerland. *Emerg Infect Dis* 2011; 17:1074-1078.
4. Caron M, Bouscaillou J, Kazanji M. Acute risk for hepatitis E virus infection among HIV-1-positive pregnant women in central Africa. *Virology* 2012 31; 9:254.
5. Alavian SM, Fallafian F, Lankarani KB. Epidemiology of Hepatitis E in Iran and Pakistan. *Hepat Mon* 2009; 9: 60-65.
6. Keyvani H, Shahrabadi MS, Najafifard S, Hajibeigi B, Fallahian F, Alavian M. Seroprevalence of anti-HEV and HEV RNA among volunteer blood donors and patients with Hepatitis B and C in Iran. *Bangladesh Liver Journal* 2009;1:34-37.
7. Taremi M, Gachkar L, MahmoudArabi S, Kheradpezhrouh M, Khoshbaten M. Prevalence of antibodies to hepatitis E virus among male blood donors in Tabriz, Islamic Republic of Iran. *East Mediterr Health J* 2007; 13:98-102.
8. Assarehzadegan MA, Shakerinejad G, Amini A, Rezaee SA. Seroprevalence of hepatitis E virus in blood donors in Khuzestan Province, southwest Iran. *Int J Infect Dis* 2008; 12:387-390.
9. Saffar MJ, Farhadi R, Ajami A, Khalilian AR, Babamahmodi F, SaffarH. Seroepidemiology of hepatitis E virus infection in 2-25-year-olds in Sari district, Islamic Republic of Iran. *East Mediterr Health J* 2009; 15:136-142.
10. Raofi R, Nazer MR, Pournia Y. Seroepidemiology of hepatitis E virus in Western Iran. *Braz J Infect Dis* 2012; 16:302-303
11. Taremi M, Mohammad Alizadeh AH, Ardalan A, Ansari S, Zali MR. Seroprevalence of hepatitis E in Nahavand, Islamic Republic of Iran: a population-based study. *East Mediterr Health J* 2008; 14:157-162.
12. Ataei B, Nokhodian Z, Javadi AA, Kassaian N, Shoaei P, Farajzadegan Z, et al. Hepatitis E virus in Isfahan Province: a population-based study. *Int J Infect Dis* 2009; 13:67-71.
13. Ahmadi Ghezeldasht S1, Miri R, Hedayatimoghadam M, Shamsian A, Bidkhorji H, Fathimoghadam F, et al. Population movement and virus spreading: HEV spreading in a pilgrimage city, Mashhad in Northeast Iran; an Example. *Hepat Mon* 2013; 13:e10255.
14. Ehteram H, Ramezani A, Eslamifar A, Sofian M, Banifazl M, Ghassemi S, et al. Seroprevalence of Hepatitis E Virus infection among volunteer blood donors in central province of Iran in 2012. *Iran J Microbiol* 2013; 5:172-176.
15. Rostamzadeh Khameneh Z, Sepehrvand N, KhalkhaliHR. Seroprevalence of hepatitis e among pregnant women in Uremia, Iran. *Hepat Mon* 2013; 13(11):e10931.
16. Sellier P, Mazon MC, Tesse S, Badsy E, Evans J, Magnier JD, et al. Hepatitis E virus infection in HIV-infected patients with elevated serum transami-

- nases levels. *Viol J* 2011; 8:171.
17. Ramezani A, Velayati AA, Khorami-Sarvestani S, Eslamifar A, Mohraz M, Banifazl M, et al. Hepatitis E virus infection in patients infected with human immune deficiency virus in an endemic area in Iran. *Int J STD AIDS* 2013; 24:769-774.
 18. Curry JA, Adams N, Crum-Cianflone NF. Acute Hepatitis E Virus (HEV) Infection in an HIV-Infected Person in the U.S. *Ann Intern Med* 2009; 150: 226–227.
 19. Mateos-Lindemann ML, Diez-Aguilar M, Galdamez AL, Galán JC, Moreno A, Pérez-Gracia MT. Patients infected with HIV are at high-risk for hepatitis E virus infection in Spain. *J Med Virol* 2014;86:71-74.
 20. Sharipova IN, Berezhnaya AV, Puzyrev VF, Burkov AN, Ulanova TI. Hepatitis E virus seroprevalence in patients with HIV in Nizhny Novgorod, Russia. *BMC Infect Dis* 2014; 14(Suppl 2):P100.
 21. Feldt T, Sarfo FS, Zoufaly A, Phillips RO, Burchard G, van Lunzen J, et al. Hepatitis E virus infections in HIV-infected patients in Ghana and Cameroon. *J Clin Virol* 2013; 58:18-23.
 22. Pineda JA, Cifuentes C, Parra M, Merchante N, Pérez-Navarro E, Rivero-Juárez A, et al. Incidence and natural history of hepatitis E virus coinfection among HIV-infected patients. *AIDS* 2014 ;28:1931-1937
 23. Sherman KE, Terrault N, Barin B, Rousterv SD, Shanta MT. Hepatitis E infection in HIV-infected liver and kidney transplant candidates. *J Viral Hepat* 2014; 21(8):e74-7.
 24. Crum-Cianflone NF, Curry J, Drobeniuc J, Weintrob A, Landrum M, Ganesan A, et al. Hepatitis E virus infection in HIV-infected persons. *Emerg Infect Dis* 2012; 18:502-506.
 25. Mamun-AI-Mahtab, Rahman S, Khan M, Karim F. HEV infection as an etiologic factor for acute hepatitis: experience from a tertiary hospital in Bangladesh. *J Health Popul Nutr* 2009; 27:14-19.
 26. Kuniholm MH, Labrique AB, Nelson KE. Should HIV-infected patients with unexplained chronic liver enzyme elevations be tested for hepatitis E virus? *Clin Infect Dis* 2010 ; 50:1545-1546.
 27. Colson P, Dhiver C, Gérolami R. Hepatitis E virus as a newly identified cause of acute viral hepatitis during human immunodeficiency virus infection. *Clin Microbiol Infect* 2008 Dec; 14(12):1176-80.
 28. Dalton HR, Saunders M, Woolson KL. Hepatitis E virus in developed countries: one of the most successful zoonotic viral diseases in human history? *J Virus Eradication* 2015; 1: 23–29.
 29. Dalton HR, Bendall RP, Keane FE, Tedder RS, Ijaz S. Persistent carriage of hepatitis E virus in patients with HIV infection. *N Engl J Med* 2009; 361:1025-1027.