Original Article

Prevalence of Seropositive and Seronegative Chronic HCV Infections in Southern Thai HIV Patients

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Objective: Hepatitis C virus [HCV] shares common transmission pathways with human immunodeficiency virus [HIV]. HIV-HCV co-infection is associated with negative impacts on both HIV and HCV when compare with mono-infection. Anti-HCV test is the main screening method for HCV infection. However, in HIV patients, false-negative anti-HCV may occur as a result of impaired immunity, and HCV RNA may be the sole investigation to diagnose HCV infection in those patients. Data regarding prevalences of both seropositive (anti-HCV+) and seronegative HCV (anti-HCV- but HCV RNA+) infection in HIV individuals in Thailand are limited. The aims of this study are to define the prevalence of seropositive and seronegative HCV infection in Southern Thai HIV patients.

Materials and Methods: This is a cross-sectional study in 2 centers in Southern Thailand: Songklanagarind and Songkhla Hospital. Inclusion criteria were known adult HIV patients with available CD_4 count within 6 months of enrollment. Exclusion criteria were patients with coexisting autoimmune disease, renal dialysis, immunosuppressive therapy including corticosteroids treatment, and history or clinical condition that cannot exclude acute HCV infection. Plasma samples were obtained from all eligible patients and test for anti-HCV (third-generation enzyme immunoassay) and HCV RNA.

Results: A total of 117 HIV patients were enrolled, with mean age of 44 years and 51.3% were male. The median CD_4 level was 524 cells/mm^3. The major HIV transmission route was heterosexual (83.8%), and intravenous drug use [IVDU] was found 3.42% of patients. Nine patients (7.7%) were positive for anti HCV and, among those, HCV RNA was detectable in 8 patients (6.8%). However, no HCV RNA was detected in all patients with negative anti-HCV. When compared with no HCV co-infection group, lower CD_4 count (343 vs. 549 cells/mm^3; $p = 0.035$), more IVDU (33.3% vs. 0.9%, $p = 0.001$), lower heterosexual as a route of transmission (55.6% vs. 86.1%, $p = 0.037$), and more elevated aspartate aminotransferase [AST] level (31 vs. 24 U/L, $p = 0.019$) were observed in seropositive HCV group.

Conclusion: The prevalence of seropositive HCV infection in Southern Thai HIV patients was 7.7%. Low CD_4 count, IVDU and elevated AST were significantly associated with HCV co-infection. No seronegative HCV infection was detected in our HIV patients.

Keywords: Hepatitis C, Seropositive, Seronegative, HIV, Negative anti-HCV, HCV infection, Chronic HCV, AIDS, Co-infection

J Med Assoc Thai 2018; 101 (Suppl. 4): S72-S79
Full text. e-Journal: http://www.jmatonline.com

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How to cite this article: Durongpongkasem P,Sripongpun P,Chamroonkul N,Kositpantawong N,Ruangchan S,Jarumanokul R,Kongkamol C,Piratvisuth T. Prevalence of seropositive and seronegative chronic HCV infection in Southern Thai HIV patients. J Med Assoc Thai 2018;101;Suppl.4:S72-S79.

Human immunodeficiency virus [HIV] and hepatitis C virus [HCV] infections are global public health problems[1]. Thirty-five million people were estimated to be infected with HIV globally, and about 180 million people for HCV infection worldwide[2,3]. HCV and HIV share common transmission pathways which may explain the high rate of co-infection between these 2 viruses. It was estimated that 4 to 5 million individuals (11% to 14% of all HIV patients) have concomitant HCV co-infection[4]. Despite both of them are transmitted via blood contact, HCV infection are more common in transfusion of blood components, intravenous drug users [IVDU] rather than sexual, and mother-to-child transmission[5].

Comparing with either HIV or HCV mono-infection, HIV/HCV co-infection results in more severe clinical outcomes than mono-infected patients[6]. Impacts of HIV on HCV infection are accelerated progression of HCV-related liver diseases, especially in patients with low CD_4 count, and high HIV viral load[7,8]. HCV also adversely affects progression of HIV disease. Liver disease is a leading cause of mortality for HIV-infected individuals in the antiretroviral therapy era. Patients with co-infection have shorter median survival times than patients with HIV mono-infection[9-11].

Aside from negative impacts on clinical outcomes, HIV/HCV co-infection was also previously known as 'difficult-to-treat' population among all HCV patients in the era of peg-interferon/ribavirin therapy. Long duration of treatment for all HCV genotypes, and selective high CD_4 count HIV hosts were needed, yet thesustained virological response [SVR] rates were not satisfactory high in this group of patients. However, with the discovery of novel HCV 'direct antiviral agents [DAA]', nowadays, current treatment of HIV/HCV co-infection with DAAs exhibits remarkably high SVR rates (>90%), comparable to treatment outcomes of HCV mono-infection. Making this group of patients should be identified and treated[12-21].

To identify patients with HIV/HCV co-infection, there are some considerations in this subgroup of patients. In general population, antibody testing (anti-HCV) is the main screening method for HCV infection, which high sensitivity and specificity were demonstrated[22-26]. Nevertheless, HCV serological screening in HIV-infected patients may not be the optimal method. Chronic HCV viremia (detectable HCV RNA) in the absence of HCV antibody, or so-called "seronegative HCV" were addressed in patients with HIV infection, hemodialysis, and organ transplantation[27-30]. Immunosuppression by HIV infection may impair antibody formation and results in false negative HCV antibody tests[12,16]. Prevalence of false-negative anti-HCV by enzyme-linked immunosorbent assay [ELISA], or seronegative HCV, were reported by several studies in range from 1.3 to 38.2%[31-39].

Given the clinical significance of HCV co-infection, experts and national guidelines including American Association for the Study of Liver Diseases [AASLD], European Association for the Study of the Liver [EASL], Infectious Diseases Society of America [IDSA], and Thai Association for the Study of the Liver [THASL] recommend HCV RNA testing in HIV patients with suspected chronic liver disease whose anti-HCV results are negative[40-42]. But data regarding prevalence of both seropositive and seronegative HCV infection in Thai HIV patients are limited.

In this study, we aim to define the prevalence of seropositive and seronegative chronic HCV infections in Thai HIV patients.

Materials and Methods

We conducted a cross-sectional study at the Infectious Diseases Clinic in 2 centers: Songklanagarind, and Songkhla Hospital, which located in different districts of the same province; Songkhla, in Sounthern Thailand. Songklanagarind Hospital is a tertiary care hospital and the only university hospital in Southern Thailand, whereas Songkla Hospital is a secondary care hospital. The study was performed from August to November, 2016. Inclusion criteria were: known HIV patients, age of at least 18 years, with available CD_4 count within 6 months of enrollment, and never underwent HCV RNA testing before enrollment. Exclusion criteria were: patients with coexisting autoimmune disease, renal dialysis, immunosuppressive therapy including corticosteroids treatment, and history or clinical condition that cannot exclude acute HCV infection; as the above-mentioned patients could have false negative anti-HCV results themselves.We also excluded patients who were already known as HIV/HCV co-infection before enrollment, and patients who refused to participate in the study.

Baseline characteristics such as, but not limit to, gender, age, and route of HIV transmission were collected. Laboratory data of CD_4 level within 6 months of enrollment and liver function test were also collected. Patients without previous anti-HCV result within 6 months of enrollment would underwent both anti-HCV, and HCV RNA testing; while patients with known being

negative for anti-HCV, plasma samples would be obtained only for HCV RNA level.

Plasma samples were consecutively obtained from all eligible patients at the time of OPD encounter. Serum creatinine, liver function test were evaluated from laboratory centers in both hospitals. Samples for anti-HCV and HCV RNA testing were stored at -20°C for <14 days. HCV antibody tests were performed by a third-generation assay (Abbott ARCHITECT anti-HCV chemiluminescent microparticle immunoassay) which detects multiple antigenic determinants (core, NS3, NS4 and NS5). HCV RNA amplification was done by COBAS® AmpliPrep/COBAS® TaqMan® HCV Test with a detection limit of less than 15 IU/mL.

Informed consent was obtained from all patients and this study was approved by Human Research Ethics Committees [HREC] at Faculty of Medicine, Prince of Songkla University.

Statistical analysis

Data were expressed as mean and standard deviation [SD], or median and interquartile range [IQR] regarding distribution of the data. Prevalence was calculated in percentage. Categorical variables were compared by Chi-square test or Fisher's exact test, whereas Wilcoxon rank-sum test or Student's t-test was used for comparison of continuous variables. The percentages were expressed with 95% confidence interval (95% CI). Comparison values with $p<0.05$ were considered statistically significant. The R version 3.3.1 (The R Foundation for Statistical Computing Platform) was used for analysis.

Results

Study population

Of 138 patients who were screened, 21 patients were excluded, and a total of 117 HIV-positive patients were enrolled in this study (Figure 1). Baseline characteristics of the eligible patients are shown in Table 1. The mean age of patients was 44 years old with slightly male predominance. The mean CD_4 level was high and most of the patients were on antiretroviral therapy. The major HIV transmission route was heterosexual (83.8%), and intravenous drug use [IVDU] was found in 3.42% of patients.

Seropositive and seronegative HCV infection in HIV patients

Nine patients (7.7%) were positive for anti-HCV (seropositive HCV), and HCV viremia were detectable in 8 of 9 patients (6.8%). However, no HCV

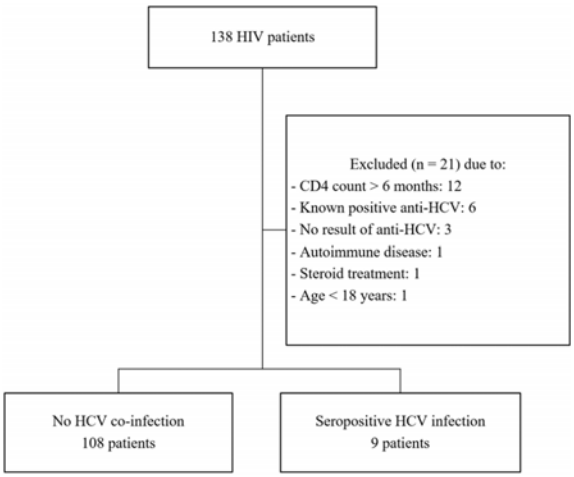

Figure 1 Study population.

Table 1. Baseline characteristics of all eligible HIV patients

Characteristics	Patients (n = 117)
Age (year)	44.1±10.3
Male	60 (51.3)
BMI (kg/m^2)	22.1±3.4
Smoking	25 (21.4)
Alcoholic drinking	21 (17.9)
Comorbidities	
Ischemic heart disease	2 (1.7)
Chronic lung disease	1 (0.8)
Chronic kidney disease	3 (2.5)
Diabetes mellitus	9 (7.6)
Hypertension	8 (6.8)
CD_4 count (cells/mm^3)	533±281.4
Antiretroviral therapy	109 (93.1)
HIV transmission route	
IVDU	4 (3.4)
Heterosexual	98 (83.8)
Homosexual	12 (10.3)
Blood transfusion	2 (1.7)
Mother-to-child	1 (0.8)
Tattooing	2 (1.7)
AST (U/L	29.7±19.7
ALT (U/L)	30.4±22.6
Serum creatinine (mg/dL)	0.89±0.5

ALT = alanine aminotransferase; AST = aspartate aminotrans ferase; BMI = body mass index; HIV = human immuno-deficiency virus; IVDU = intravenous drug use

* Data are expressed as number (%) or mean ± standard deviation.

RNA was detected in all patients with negative anti-HCV, making prevalence of seronegative HCV infection in our study was zero. High HCV viral loads (≥100,000 IU/mL) were detected among all HCV viremia patients. Comparing with HIV patients without HCV co-infection, patients with seropositive HCV had a significant lower CD_4 count, higher AST level, and more IVDU and less heterosexual as risks of HIV transmission (Table 2).

Discussion

The present study is the first study to define prevalence of both seropositive and seronegative HCV infection in Thai HIV patients. Our study shows that 7.7% of Southern Thai HIV patients were positive for anti-HCV, and true HCV viremia were observed in all but one patients. The prevalence of seropositive HCV infection among HIV patients in our study was almost identical to previous studies in Central Thailand (7.7% to 7.8%)[43,44], and it was much greater than the prevalence of HCV monoinfection in general Thai population (0.98% to 2.9%)[45,49], as HIV and HCV share common routes of transmission. However, the prevalence of HCV and HIV co-infection in Thailand was much lower than US and European countries (17% to 33%)[4,47]. This result indicates that the transmittal efficiency may differ between each viruses despite similar transmission. The majority proportion of HCV spread through exposure to contaminated blood products, especially in IVDU patients, while sexual transmission of HCV is quite low. The main HIV risk factor of patients in our study was heterosexual, whereas IVDU was the main route of transmission of HIV in the US and European studies[4,47].

In the present study, we demonstrated that factors associated with the presence of seropositive HCV co-infection among HIV patients are; lower CD_4 count, IVDU as an HIV risk factor, and more elevated AST level when comparing to HIV mono-infection. These are in contrast to the previous study in Thailand by Phuangchoei et al[43], which no associated factor of

Table 2. Comparison of parameters between HIV patients with and without HCV co-infection

	No HCV co-infection (n = 108)	HCV co-infection (n = 9)	*p*-value
Age (year), mean ± SD	44.5±10.3	39.9±11.5	0.200
Male	53 (49.1)	7 (77.8)	0.164
BMI (kg/m^2), median (IQR)	21.8 (20.2, 23.9)	19.6 (17.6, 22.4)	0.051
Smoking	22 (20.4)	3 (33.3)	0.605
Alcoholic drinking	20 (18.5)	1 (11.1)	0.607
Comorbidities			
Ischemic heart disease	1 (0.9)	1 (11.1)	0.149
Chronic lung disease	1 (0.9)	0	1
Chronic kidney disease	3 (2.8)	0	1
Diabetes mellitus	8 (7.4)	1 (11.1)	0.526
Hypertension	6 (5.6)	2 (22.2)	0.116
CD_4 count (cells/mm^3), mean ± SD	549.2±276.5	343.6±286.2	0.035
Antiretroviral therapy	102 (94.4)	7 (77.8)	0.116
HIV transmission route			
IVDU	1 (0.9)	3 (33.3)	0.001
Heterosexual	93 (86.1)	5 (55.6)	0.037
Homosexual	10 (9.3)	2 (22.2)	0.231
Blood transfusion	2 (1.9)	0	1
Mother-to-child	1 (0.9)	0	1
Tattooing	1 (0.9)	1 (11.1)	0.149
AST (U/L), median (IQR)	24.5 (20, 34.8)	31 (29.2, 43.5)	0.019
ALT (U/L), median (IQR)	23 (17, 37.2)	34 (20, 38)	0.262
Serum creatinine (mg/dL), median (IQR)	0.8 (0.6, 1)	0.8 (0.7, 0.9)	0.861

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQR = interquatile range; IVDU = itravenous drug use
Data are expressed as number (%) except being specified.

HIV-HCV co-infection could be observed. Nonetheless, our study results are concordant with the earlier studies in other countries that low CD_4 count[4,48,49], IVDU[4,48-50], and elevated liver enzymes[49] were associated with HCV co-infection among HIV patients.

Meanwhile, seropositive HCV data in our study are akin to the previous studies as mentioned above, the data regarding seronegative HCV infection in HIV patients in our study is different. In preceding studies, the prevalence of HCV viremia without detectable anti-HCV antibodies (as known as seronegative HCV infection) in HIV patients varies from 1.3% to 38.2%[31-39]. Abnormal antibody production and cellular immune responses to HCV had been described in HIV patients with seronegative HCV infection[51-54]. In contrast to our study, no detectable HCV viremia was found in HIV patients with negative HCV antibodies by third-generation assay.

To explain the surprisingly dissimilarity results between the present study and the previous studies by Hadlich et al and George et al, whose HCV antibody tests were performed by the same generation of enzyme immunoassay method, and seronegative HCV prevalence were 8.3% and 20%, respectively, the differences in baseline characteristics of the HIV patients may play a significant role for such results. Baseline mean CD_4 counts of the patients in our study (533 cells/mm^3) is higher than in Hadlich et al and George et al (31 and 225 cells/mm^3, respectively[31,39]. The other factor that might explain the very low prevalence of seronegative HCV in our population is the distinction of HIV transmission routes among study populations. Thio et al demonstrated 8.3% prevalence of seronegative HCV in high CD_4 HIV patients[33] but all of the patients in their study had history of IVDU. Another study from Juniastuti[32] reported the prevalence of seronegative HCV infection in HIV patients was 38.2% and one-third of the population in their study was IVDU. The major route of HIV transmission in our study was heterosexual (>80%) and IVDU was found in only 3.4%.

The limitations of our study are small sample size, and was conducted in the secondary and tertiary care settings, which may not reflect the whole population of Southern Thai HIV patients. Nevertheless, it depicts the real situation of HIV patients in HAART era.

Conclusion

The prevalence of seropositive HCV infection in Southern Thai HIV patients was 7.7%. Low CD_4 count, IVDU and elevated AST were significantly associated with HCV co-infection. No seronegative HCV infection was detected in our HIV patients. Despite the theoretical assumption that impaired immunity in HIV patients has an impact on anti-HCV production, we suggest that HCV RNA should not be tested in every HIV patients with negative anti-HCV. To minimize the unnecessary cost, HCV RNA testing should be evaluated only in high-risk for HIV/HCV co-infection e.g. Low CD4 count, IVDU, and abnormal liver enzymes. Further cost effectiveness data regarding this issue is needed.

What is already known in this topic?

HIV and HCV share common routes of transmission, making co-infection is not uncommon, and resulting in more severe outcomes compared with mono-infection. In HIV patients, false-negative anti-HCV may occur as a result of impaired immunity, and HCV RNA may be the sole investigation to diagnose HCV infection in those patients, or so-called 'seronegative HCV'. Prevalence of seronegative HCV in HIV patients were reported by several studies in range from 1.3% to 38.2%. There is no data in Thailand

What this study adds?

In our study population (from 2 centers in Southern Thailand), the prevalence of seropositive HCV in HIV patients was 7.7% and associated with lower CD_4 count, history of IVDU, and elevated AST level when compared with no HCV co-infection HIV patients. There was no case of seronegative HCV in our study.

Acknowledgement

The authors are grateful to all participants in this study. The research was supported by grants from Faculty of Medicine, Prince of Songkla University, Thailand, and The Gastroenterological Association of Thailand (GAT).

Potential conflicts of interest

None.

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