Clinical Characteristics of Hepatitis B and C Virus Infections in HIV-Infected Patients

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Background: *Hepatitis B virus (HBV) and hepatitis C virus (HCV) share a common route of transmission with human immunodeficiency virus (HIV). HIV co-infected with HBV or HCV was associated with a progression to severe liver disease, increased risk of hepatotoxicity from antiretroviral therapy and reduced survival. Data regarding HBV and HCV infection in HIV-positive individuals in Thailand is limited.*
Objectives: *To investigate the prevalence and clinical characteristics of HBV and HCV infection in HIV-infected patients in Siriraj Hospital.*
Material and Method: *A retrospective study was conducted in adult HIV-positive followed up at the Infectious Disease Clinic, Siriraj Hospital. Prevalence of HBV and HCV infections and clinical characteristics were analyzed.*
Results: *250 HIV-positive patients were enrolled, mean age was 38.8 years and 57.2% were male. HBV infection was found in 6.5% (15/231), and HCV infection was 7.7% (17/222). One patient had both HBV and HCV infections. In multivariate analysis, factors associated with either HBV or HCV co-infection included male gender (77.4% vs. 55%; p 0.008), history of salmonellosis (9.7% vs. 2.5%; p 0.042) or elevated serum alanine aminotransferase (ALT) level (34 U/L vs. 25 U/L; p 0.018). Factors associated with HBV infection, compared with those without hepatitis virus infection, included male gender (86.7% vs. 56%; p 0.038), history of salmonellosis (20% vs. 2.3%; p 0.005), elevated serum ALT level (42 U/L vs. 25 U/L; p 0.012) and low CD_4 percent (1.05% vs. 5.02%; p 0.04). In this study, we did not find any factor associated with HCV infection in HIV patients.*
Conclusion: *The prevalence of HBV and HCV infection in HIV-infected Thai patients is significant. Male gender, history of salmonellosis, elevated serum ALT levels, and low CD_4 percent are associated with HBV co-infection.*

Keywords: *HIV infection, Hepatitis B, Hepatitis C, HBV, HCV, AIDS*

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Hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) can be transmitted via similar modes, such as intravenous drug use (IVDU), blood transfusion or maternal-to-child transmission. Co-infection of HIV and HBV or HCV was associated with increased risk of progression to severe liver diseases and hepatotoxicity from antiretroviral therapy (ART)[1]. In addition, viral hepatitis has been shown to be associated with reduced survival in HIV-infected individuals[1,2]. In the United States and European countries, the prevalence of HBV and HCV infections in HIV-infected patients is 5-15% and 33%, respectively[1]. HIV infection is associated with both failure to seroconvert following acute HBV infection, and a greater risk of developing chronic hepatitis, compared with HIV-negative individuals. Chronic HBV infection may complicate ART by increasing risk of drug-induced hepatotoxicity. Liver-related mortality was more than three times higher in HBsAg-positive HIV-infected patients, compared with those without HBV infection[2].

HIV infection exacerbates the natural history of HCV infection. In fact, HIV-infected patients are less likely to clear hepatitis C viremia following acute infection, resulting in a higher HCV RNA loads. Compared with HIV-negative individuals, HIV-infected patients are likely to progress to HCV-related liver disease more rapidly[3]. Therefore, HIV/HCV

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co-infection increased risk of cirrhosis 2.07 times more than in those with HCV monoinfection[4].

Thai national guidelines on HIV/AIDS recommend screening all HIV-infected persons for HBV and HCV[5]. Knowing the prevalence of HBV and HCV infection is essential for planning of patient care and to prevent liver injury. Data regarding HBV and HCV infections in HIV-positive individuals in Thailand are limited. This study aims to investigate the prevalence and clinical characteristics of HBV and HCV infections in HIV-positive patients.

Material and Method

Patients

The authors performed a retrospective analysis of adult HIV-positive patients receiving highly active antiretroviral therapy (HAART) at the Infectious Disease Clinic, Siriraj Hospital, between 2002-2011. Subjects were aged 18 years or more. Data on HBV and HCV serologies (HBsAg and HCV antibodies, respectively) were recorded. The hospital records were systematically reviewed by using a standardized protocol to assess their demographic and clinical features, which included the basic characteristics such as age, sex, comorbid diseases, history of opportunistic infections and laboratory tests. Initial serum alanine aminotransferase (ALT) and CD_4 counts at the time of starting HAART were collected. The study was approved by Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital.

Statistical analysis

Data were analyzed using mean or median, and frequency (%) for continuous and categorical variables, respectively. Prevalence of co-infection and its 95% confidence interval were calculated. Chi-square test, Fisher's exact test, Student t-test, or Mann-Whitney U test were used for statistical evaluation, where appropriate. All tests were two-sided and the threshold for statistical significance was established at a p-value <0.05. Factors with p-value <0.2 in univariate analysis were included in multivariate analysis using multiple logistic regression analysis (backward stepwise). The statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

There were 250 HIV-positive patients enrolled, mean age was 38.8 years and 57.2% were male. HBV infection was found in 6.5% (15/231), and HCV infection was 7.7% (17/222). One patient had both HBV and HCV infection. Baseline characteristics of the patients were shown in Table 1. History of opportunistic infections was found in 66.4%. CD_4 T-lymphocyte count ranged from 1 to 735 cells/mm^3 (median = 51 cells/mm^3).

Factors associated with either HBV or HCV co-infection are shown in Table 2. The independent factors in multivariate analysis included male gender,

Table 1. Demographic data and clinical characteristics of 250 HIV-positive patients in this study

Baseline characteristics	Number (%) or median (min-max)
Mean age ± SD, year	38.8±10.6
Male gender	143 (57.2)
Comorbid disease	37 (14.8)
Diabetic mellitus	7 (2.8)
Hypertension	17 (6.8)
Dyslipidemia	8 (3.2)
Cerebrovascular accident	2 (0.8)
Coronary artery disease	1 (0.4)
Chronic kidney disease	1 (0.4)
Cirrhosis	2 (0.8)
Malignancy*	7 (2.8)
History of opportunistic infection	166 (66.4)
Tuberculosis and other mycobacterium	86 (34.4)
Pneumocystis pneumonia	60 (24.0)
Cryptococcosis	20 (8.0)
Cytomegalovirus disease	19 (7.6)
Mycobacterium avium complex	9 (3.6)
Salmonellosis	8 (3.2)
Isosporiasis	6 (2.4)
Histoplasmosis	4 (1.6)
Cryptosporidiosis	3 (1.2)
Penicillosis	2 (0.8)
Candidiasis	2 (0.8)
Kaposi's sarcoma	1 (0.4)
Invasive cervical cancer	1 (0.4)
Herpes simplex infection	1 (0.4)
Microsporidiosis	1 (0.4)
Toxoplasmosis	0 (0)
Aspartate aminotransferase (AST), U/L	35.0 (11-1,873)
Alanine aminotransferase (ALT), U/L	28.5 (3-2,072)
Alkaline phosphatase (ALP), U/L	92.0 (28-1,032)
Total bilirubin, mg/dL	0.4 (0.1-25.5)
Direct bilirubin. mg/dL	0.1 (0.0-18.4)
CD_4 cell count, cells/mm^3	51.0 (1-735)
$\%CD_4$	4.6 (0.06-37.69)
Viral load, copies/mm^3	273,298.5 (40-3,821,226)

* Malignancy (7 patients; 2 cervical carcinoma, 2 lymphoma, 1 hepatocellular carcinoma, 1 nasopharyngeal carcinoma, 1 angiofollicular lymph node hyperplasia)

Table 2. Factors associated with HBV or HCV co-infection in HIV-positive patients in univariate analysis

Factor	Number (%) or median (min-max)		*p*-value	Crude OR (95% CI)
	No co-infection (n = 200)	HBV or HCV co-infection (n = 31)		
Mean age ± SD, year	38.9±11.1	38.2±8.1	0.66	0.99 (0.96-1.03)
Male gender	110 (55.0)	24 (77.4)	0.02*	2.81 (1.16-6.81)
Comorbid disease	30 (15.0)	5 (16.1)	0.79	1.09 (0.39-3.06)
History of OIs	130 (65.0)	21 (67.7)	0.77	1.13 (0.50-2.54)
TB and other mycobacteria	65 (32.5)	13 (41.9)	0.30	1.50 (0.69-3.25)
PCP	50 (25.0)	4 (12.9)	0.14	0.44 (0.15-1.33)
Cryptococcosis	15 (7.5)	2 (6.5)	1.00	0.85 (0.19-3.91)
CMV	15 (7.5)	2 (6.5)	1.00	0.85 (0.19-3.91)
MAC	7 (3.5)	2 (6.5)	0.35	1.90 (0.38-9.60)
Salmonellosis	5 (2.5)	3 (9.7)	0.08	4.18 (0.95-18.45)
Histoplasmosis	3 (1.5)	1 (3.2)	0.44	2.19 (0.22-21.74)
Penicillosis	1 (0.5)	1 (3.2)	0.25	6.63 (0.40-108.89)
AST, U/L	35 (14-196)	37 (11-1,873)	0.07*	1.01 (0.99-1.02)
ALT, U/L	25 (3-207)	34 (5-2,072)	0.03*	1.01 (1.00-1.02)
ALP, U/L	88 (28-1,032)	83 (46-360)	0.95	1.00 (0.99-1.00)
Total bilirubin, mg/dL	0.4 (0.1-3.8)	0.5 (0.2-25.5)	0.05*	2.19 (1.02-4.70)
Direct bilirubin, mg/dL	0.1 (0.0-0.7)	0.1 (0.0-18.4)	0.01*	17.30 (1.84-62.52)
CD_4 cell count, cells/mm^3	56 (1-735)	43 (2-531)	0.24	0.99 (0.99-1.00)
%CD_4	5.3 (0.1-37.7)	3.3 (0.3-36.2)	0.08*	0.97 (0.91-1.04)
Viral load, copies/mm^3	287,000 (40-3,821,226)	87,024 (38,026-1,870,000)	0.76	1.00 (1.00-1.00)

HBV = hepatitis B virus; HCV = hepatitis C virus; OIs = opportunistic infections; TB = tuberculosis; PCP = *Pneumocystis carinii* pneumonia; CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex
* Factors with *p*-value <0.2 were included in multiple logistic regression analysis

Table 3. Factors associated with HBV or HCV co-infection in HIV-infected patients in multivariate analysis

Factor	Adjusted odd ratio	95% CI	*p*-value
Male gender	5.78	1.60-20.83	0.01
Salmonellosis	8.63	1.08-68.70	0.04
ALT	1.01	1.00-1.01	0.02
%CD_4	0.93	0.84-1.03	0.14

history of salmonellosis and elevated serum ALT level (Table 3). When we analyzed the factors associated with HBV co-infection only, compared with those without hepatitis virus infection (Table 4), The authors found that the independent factors in multivariate analysis included male gender, history of salmonellosis, elevated serum ALT level and CD_4 percentage (Table 5). In the present study, the authord did not find any factor associated with HCV infection in HIV-infected patients as shown in Table 6.

Discussion

The present study found that the prevalence of HBV or HCV co-infected with Thai HIV were 6.5% and 7.7%, respectively. The prevalence of HBV infection in the general Thai and Asian population from previous studies was between 9.8-10%[6,7]. The prevalence of HBV infection in HIV-infected patients from this study was slightly lower than that of a previous study conducted in 2003 at Ramathibodi Hospital, which was 8.7%[8]. Regarding the prevalence of HCV co-infection in HIV-positive patients, it was quite similar to the previous study, which was 7.8%[8]. When compared with the prevalence of HCV monoinfection in the general Thai population (0.98% to 2.9%)[9,10], it was much higher. However, HCV/HIV co-infection in our study was not as high as those in the United States and European countries, which was about 33%[1]. In Thailand, the major route of HIV transmission was sexual contact but the most important mode of transmission of HCV is IVDU[1]. This may partly explain the relatively lower prevalence of HCV/HIV co-infection in Thai population[11].

The authors found that male gender, history of salmonellosis, and elevated ALT were independently associated with either HBV/HIV or HCV/HIV co-infection. All those factors, with an additional factor of CD_4 percentage were associated with HBV/HIV co-infection. Previous study also demonstrated

Table 4. Factors associated with HBV co-infection in HIV-positive patients in univariate analysis

Factor	Number (%) or median (min, max)		*p*-value	Crude OR (95% CI)
	No HBV co-infection (n = 216)	HBV co-infection (n = 15)		
Mean age ± SD, year	38.6±10.9	41.7±8.0	0.29	1.03 (0.98-1.07)
Male gender	121 (56.0)	13 (86.7)	0.02*	5.10 (1.12-23.17)
Comorbid disease	33 (15.3)	2 (13.3)	1.00	0.85 (0.18-3.96)
History of OIs	141 (65.3)	10 (66.7)	0.91	1.06 (0.35-3.23)
TB and other mycobacteria	72 (33.3)	6 (40.0)	0.60	1.33 (0.46-3.89)
PCP	53 (24.5)	1 (6.7)	0.20	0.22 (0.03-1.71)
Cryptococcosis	15 (6.9)	2 (13.3)	0.30	2.06 (0.43-9.99)
CMV	17 (7.9)	0 (0)	0.61	-
MAC	9 (4.2)	0 (0)	1.00	-
Salmonellosis	5 (2.3)	3 (20.0)	0.01*	10.55 (2.25-49.46)
Histoplasmosis	3 (1.4)	1 (6.7)	0.24	5.07 (0.50-51.96)
Penicillosis	1 (0.5)	1 (6.7)	0.13	15.36 (0.91-258.69)
AST, U/L	35 (11-680)	43 (23-1,873)	0.09*	1.00 (0.99-1.01)
ALT, U/L	25 (3-860)	42 (11-2,072)	0.01*	1.00 (1.00-1.01)
ALP, U/L	88 (28-1,032)	83 (46-283)	0.76	1.00 (0.99-1.01)
Total bilirubin, mg/dL	0.4 (0.1-3.8)	0.6 (0.3-25.5)	0.36	1.54 (0.61-3.90)
Direct bilirubin, mg/dL	0.1 (0.0-2.5)	0.2 (0.0-18.4)	0.28	2.18 (0.53-8.98)
CD_4 cell count, cells/mm^3	56 (1-735)	17 (4-531)	0.07*	1.00 (0.99-1.00)
$\%CD_4$	5.0 (0.1-37.7)	1.05 (0.5-36.2)	0.02*	1.00 (1.00-1.07)
Viral load, copies/mm^3	287,000 (40-3,821,226)	87,024 (40,305-1,870,000)	0.73	1.00 (1.00-1.00)

OIs = opportunistic infections; TB = tuberculosis; PCP = *Pneumocystis carinii* pneumonia; CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex

* Factors with *p*-value <0.2 were included in multiple logistic regression analysis

Table 5. Factors associated with HBV co-infection in HIV-infected patients in multivariate analysis

Factor	Adjusted odd ratio	95% CI	*p*-value
Male gender	16.67	1.17-250.00	0.04
Salmonellosis	56.97	3.48-932.34	0.01
ALT	1.01	1.00-1.01	0.01
$\%CD_4$	0.78	0.61-0.99	0.04

the association between male and HBV/HIV co-infection[12]. This may be explained by the fact that HBV is most often transmitted by sexual contact (both heterosexual and homosexual), followed by IVDU, in which 94% of intravenous drug users in Thailand were male[13]. Our results revealed that salmonellosis was an independent factor that highly associated with hepatitis virus infection. This could be the effect of a relatively lower CD_4 count in HIV-infected patients.

HIV-positive patients with HBV infection who received HAART had a significantly higher serum ALT. This finding was most likely caused by the hepatotropic characteristic of HBV. Therefore, HIV-infected patients with elevated ALT should be aware for HBV co-infection. In addition, the authors found that HIV-positive patients with HBV co-infection had a lower initial CD_4 percentage before starting HAART, compared with those without HBV co-infection. This finding may implies that HBV infection could be a factor that adversely affects the immune status of HIV-infected patients. Because this study was a retrospective study, we cannot establish an exact temporal relationship between HBV infection and the CD_4 level.

In conclusion, the prevalence of HBV and HCV infection in HIV-infected Thai patients is significant. Male gender, elevated serum ALT levels, history of salmonellosis and low CD_4 percent are associated with HBV co-infection.

What is already known on this topic?

The prevalence of HBV and HCV infection in HIV-infected patients is high. Elevated ALT is associated with HIV/HBV or HIV/HCV co- infection.

What this study adds?

Salmonellosis is another factor associated with HBV or HCV infection in HIV-infected patients. Future study may be warranted.

Table 6. Factors associated with HCV co-infection in HIV-positive patients (univariate analysis)

Factor	Number (%) or median (min, max)		*p*-value	Crude OR (95% CI)
	No HCV co-infection (n = 205)	HCV co-infection (n = 17)		
Mean age ± SD, year	39.2±11.1	35.5±7.1	0.06	0.97 (0.92-1.02)
Male gender	118 (57.6)	12 (70.6)	0.30	1.77 (0.60-5.21)
Comorbid disease	32 (15.6)	3 (17.6)	0.74	1.16 (0.32-4.30)
History of OIs	134 (65.4)	12 (70.6)	0.66	1.27 (0.43-3.75)
TB and other mycobacteria	67 (32.7)	8 (47.1)	0.23	1.83 (0.68-5.00)
PCP	50 (24.4)	3 (17.6)	0.77	0.66 (0.18-2.41)
Cryptococcosis	17 (8.3)	0 (0)	0.37	-
CMV	14 (6.8)	2 (11.8)	0.35	1.82 (0.38-8.76)
MAC	7 (3.4)	2 (11.8)	0.15	3.77 (0.72-19.77)
Salmonellosis	7 (3.4)	0 (0)	1.00	-
Histoplasmosis	4 (2.0)	0 (0)	1.00	-
Penicillosis	2 (1.0)	0 (0)	1.00	-
AST, U/L	35 (14-1,873)	40 (11-680)	0.29	1.00 (0.99-1.00)
ALT, U/L	28 (3-2,072)	30 (5-860)	0.52	1.00 (0.99-1.00)
ALP, U/L	89.0 (28-1,032)	107.5 (46-360)	0.71	1.00 (0.98-1.01)
Total bilirubin, mg/dL	0.4 (0.1-25.5)	0.4 (0.2-3.4)	0.47	1.03 (0.83-1.28)
Direct bilirubin, mg/dL	0.1 (0.0-18.4)	0.1 (0.0-2.5)	0.15	1.07 (0.82-1.39)
CD_4 cell count, cells/mm^3	56.5 (1-735)	59.0 (2-389)	0.75	1.00 (0.96-1.01)
%CD_4	5.4 (0.06-37.69)	3.7 (0.33-19.00)	0.49	0.97 (0.88-1.06)
Viral load, copies/mm^3	299,000 (40-3,821,226)	539,000 (38,026-750,000)	0.75	1.00 (1.00-1.00)

OIs = opportunistic infections; TB = tuberculosis; PCP = *Pneumocystis carinii* pneumonia; CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex

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Potential conflicts of interest

None.

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ลักษณะทางคลินิกของโรคไวรัสตับอักเสบบีและซีในผู้ป่วยติดเชื้อเอชไอวี

ประพินทุ์ภา พ่วงเชย, วัชรศักดิ์ โชติยะปุตตะ, เมธี ชยะกุลคีรี

ภูมิหลัง: *เชื้อไวรัสตับอักเสบบีและซี มีช่องทางการติดต่อเดียวกันกับเชื้อไวรัสเอชไอวี ผู้ป่วยที่มีการติดเชื้อไวรัสตับอักเสบบีหรือซีร่วมกับการติดเชื้อเอชไอวี มีความเสี่ยงที่จะเกิดโรคตับรุนแรงและเกิดตับอักเสบจากการรับประทานยาต้านไวรัสเพิ่ม อีกทั้งมีอัตราการรอดชีวิตลดลง ข้อมูลเกี่ยวกับการติดเชื้อไวรัสตับอักเสบบีหรือซีในผู้ป่วยติดเชื้อเอชไอวีในประเทศไทยยังมีจำกัด*

วัตถุประสงค์: *เพื่อศึกษาถึงความชุกและลักษณะทางคลินิกของโรคไวรัสตับอักเสบบีและซีในผู้ป่วยติดเชื้อเอชไอวี*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลังในผู้ป่วยติดเชื้อเอชไอวี ที่ติดตามการรักษาในคลินิกโรคติดเชื้อ โรงพยาบาลศิริราช โดยเก็บข้อมูลลักษณะทางคลินิกของผู้ป่วยติดเชื้อเอชไอวีที่มีการติดเชื้อไวรัสตับอักเสบบีหรือซีร่วมด้วย และนำไปวิเคราะห์ทางสถิติ*

ผลการศึกษา: *ผู้ป่วยติดเชื้อเอชไอวีที่ศึกษามีทั้งหมด 250 ราย อายุเฉลี่ย 38.8 ปี เป็นผู้ป่วยชายร้อยละ 57.2 ความชุกของโรคไวรัสตับอักเสบบีและไวรัสตับอักเสบซีร่วมกับติดเชื้อเอชไอวีเท่ากับร้อยละ 6.5 (15/231) และร้อยละ 7.7 (17/222) ตามลำดับ มีผู้ป่วย 1 ราย มีการติดเชื้อทั้งไวรัสตับอักเสบบีและซี ปัจจัยที่มีความสัมพันธ์กับโรคไวรัสตับอักเสบบีหรือซีในผู้ป่วยติดเชื้อเอชไอวี ได้แก่ เพศชาย (ร้อยละ 77.4 เทียบกับร้อยละ 55, ค่าพี 0.008) ประวัติติดเชื้อซัลโมเนลลา (ร้อยละ 9.7 เทียบกับร้อยละ 2.5, ค่าพี 0.042) และระดับ alanine aminotransferase (ALT) ในเลือดสูง (34 U/L เทียบกับ 25 U/L, ค่าพี 0.018) เมื่อศึกษาเฉพาะการติดเชื้อไวรัสตับอักเสบบี ปัจจัยที่มีความสัมพันธ์กับการติดเชื้อไวรัสตับอักเสบบีร่วมกับการติดเชื้อเอชไอวีคือ เพศชาย (ร้อยละ 86.7 เทียบกับร้อยละ 56, ค่าพี 0.038) ประวัติติดเชื้อซัลโมเนลลา (ร้อยละ 20 เทียบกับร้อยละ 2.3, ค่าพี 0.005) ระดับ ALT ในเลือดสูง (42 U/L เทียบกับ 25 U/L, ค่าพี 0.012) และร้อยละของซีดีโฟร์ต่ำ (ร้อยละ 1.05 เทียบกับร้อยละ 5.02, ค่าพี 0.04) จากการศึกษานี้ไม่พบปัจจัยใดเลยที่มีความสัมพันธ์กับการติดเชื้อไวรัสตับอักเสบซีในผู้ป่วยติดเชื้อเอชไอวี*

สรุป: *ความชุกของโรคไวรัสตับอักเสบบีและซีในผู้ป่วยติดเชื้อเอชไอวีในประเทศไทยมีปริมาณไม่น้อย โดยพบว่าเพศชาย ประวัติติดเชื้อซัลโมเนลลา ระดับ ALT สูง และร้อยละของซีดีโฟร์ต่ำในเลือดมีความสัมพันธ์กับไวรัสตับอักเสบบีในผู้ป่วยติดเชื้อเอชไอวี*
