Prevalence of Hepatitis B Virus and Hepatitis C Virus Co-infection with Human Immunodeficiency Virus in Thai Patients: A Tertiary-care-based Study

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Background : *Hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV share the route of transmission. HBV or HCV co-infection with HIV has been associated with a reduced survival rate, an increased risk of progression to severe liver disease, and an increased risk of hepatotoxicity associated with active antiretroviral therapy. Information regarding prevalence of HBV and HCV co-infection with HIV in Thailand is limited.*

Patients and Method : *A cross-sectional study of prevalence and risk factors of HBV and HCV co-infection in HIV-infected patients was conducted. All HIV-infected patients who were cared for in March 2003 at Ramathibodi Hospital were included.*

Results : *There were 529 HIV-infected patients with a mean age of 36.7 years and 56.5% males. Of these, 58.8% lived in Bangkok, whereas, the others were from provincial areas. Heterosexual contact were the acquisition of HIV infection in 98.1% of all patients. The prevalence of HBV infection was 8.7%, and HCV infection was 7.8%. There was no difference between the prevalence of these infections in Bangkok and provincial areas ($p = 0.115$). History of intravenous drug use was associated with both HBV and HCV co-infection ($p < 0.001$). HCV co-infection group was also associated with male gender ($p = 0.002$) and elevated serum alanine transaminase (ALT) level ($p = 0.0003$).*

Conclusions : *The prevalence of HBV and HCV co-infection with HIV in Thai patients is significant. In the author's resources-limited setting, history of intravenous drug use is a major indicator to screen for both HBV and HCV co-infection. Male gender and elevated serum ALT level are also suggestive of HCV co-infection.*

Keywords : *HBV, HCV, HIV, Co-infections*

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Hepatitis B virus (HBV), hepatitis C virus (HCV), and Human Immunodeficiency Virus (HIV) share the route of transmission. HBV or HCV co-infection with HIV has been associated with a reduced survival rate [1,2], although the results of some other studies are controversial[3-6]. HBV co-infection with HIV modifies the natural history of HBV infection, increasing the percentage of patients likely to become HBV surface antigen (HBsAg) carriers and have a slower loss of serum HbeAg[5]. For HCV, several studies have suggested that HCV infection is an independent predicting factor of mortality in HIV infection[7-9] and increases the risk of progression to severe liver disease[10-13]. In addition, HCV infection has been shown to increase the risk of hepatotoxicity associated with highly active antiretroviral therapy (HAART)[14].

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In the United States and European countries, the prevalence of HBV and HCV infection in HIV-infected patients are between 9-90% and 15-30%, respectively[1,4,15-19] Knowing the prevalence of HBV and HCV co-infection will be useful in planning for taking care of patients and doing relevant clinical research. Little information about prevalence of HBV and HCV co-infection with HIV has been reported from Thailand and other Asian countries[19]. The authors, therefore, conducted the present study to estimate such prevalence in Thai HIV-infected patients.

Patients and Method

All HIV-infected patients who visited the Infectious Diseases Clinic in Ramathibodi Hospital from 1st to 30th March 2003 were included in this cross-sectional study. The study was approved by the Ethics Committee of the Faculty of Medicine Ramathibodi Hospital. Patients were informed and gave their consent. The sera were tested for HBsAg and antibody to HCV (anti-HCV) using Axsym HBsAg version 2, the third-generation and Axsym HCV version 3.0, and microparticle enzyme immunoassay (Abbott laboratories, Abbott Park, IL). The Axsym immunoassay systems were carried out and standardized according to the manufacture's protocol. All reactive serum samples were retested.

Patients characteristics such as age, sex, resident area, sexual preference, intravenous drug use, history of jaundice, history of receiving blood transfusion were also collected. Data were described using mean (or median where appropriate) and frequency (%) for continuous and cateogorical variables, respectively. Prevalence of co-infection and its 95% confidence interval were estimated. Chi-square test (or Fisher's exact test where appropriate) were used to assess association between categorical variable and co-infection. Mann-Whitney U test was used to compare medians between groups for continuous data. All analyses were performed using STATA version 7.0. P value less than 0.05 was considered to be statistically significantly different.

Results

There were 529 patients who attended the Infectious Disease Clinic during the study period. Patients' characteristics are described in Table 1. Of these, the mean age was 36.7 $\pm$ 8.8 years and 56.5% were males. More than half of the patients (58.8%) lived in Bangkok, whereas the others were from provincial areas. Most patients (98.1%) had acquired HIV from heterosexual transmission. History of AIDS defining illness was found in 29.7% of patients. Eighty percent of the patients had received antiretroviral therapy at the time of the study. Serum CD4 cell count ranged from 2 to 1161 cells/mm^3 (median = 193 cells/mm^3).

The prevalence of HBV and HCV co-infection with HIV was estimated and described in Table 2. The authors found that HBV and HCV co-infection with HIV were 8.7% (95% CI: 6.4%, 11.4%) and 7.8 % (95% CI: 5.6%, 10.4%), respectively. Only two patients (0.4%) had both HBV and HCV co-infection with HIV. According to the patients' residential area, these corresponding prevalences were slightly higher in Bangkok than the provincial areas but not statistically significant (chi-square = 2.48, p value = 0.115).

Patients' characteristics between HBV co-infection group, HCV co-infection group, and no co-infection group were compared (Table 3). The authors found that higher age and history of intravenous drug used were significantly associated with HBV infection; sex, history of intravenous drug used, and serum alamine transaminase level were associated with HCV infection. Median serum CD4 cell count of HBV co-infection group (median = 177.5, range = 11-528) and HCV co-infection group (median = 161, range = 4-887 cells/mm^3) were lower than median CD4 cell count of the no co-infection group (median = 195,

Table 1. Characteristics of 529 HIV-infected patients in the study

Characteristics	Frequency (%) n = 529
Gender	
Male	299 (56.5)
Female	230 (43.5)
Age, mean $\pm$ SD	36.7 $\pm$ 8.8
Residential area	
Bangkok	311 (58.8)
Outside Bangkok (provincial area):-	218 (41.2)
Center	111 (21.0)
Northeast	47 (8.9)
North	27 (5.1)
South	26 (4.9)
East	7 (1.3)
Sexual preference	
Heterosexual	519 (98.1)
Homosexual	10 (1.9)
History of intravenous drug use	34 (6.4)
History of jaundice	36 (6.8)
History of receiving blood transfusion	26 (4.9)
History of AIDS defining illness	157 (29.7)
On antiretroviral therapy	412 (77.9)
Serum alanine transaminase (mean $\pm$ SD)	51.7 $\pm$ 30.2
CD4 cell count (mean $\pm$ SD)	238.7 $\pm$ 205.0

Table 2. Prevalence of HBV and HCV co-infection according to the residential areas

Residential areas	Number of patients	Co-infection			
		HBV		HCV	
		No.	Prevalence/100(95% CI)	No.	Prevalence/100(95% CI)
Bangkok	311	29	9.3 (6.3 - 13.1)*	28	9.0 (6.1 - 12.7)[1]
Provincial areas	218	17	7.8 (4.6 - 12.2)*	13	6.0 (3.2 - 10.0)[1]
Center	111	9	8.1 (3.8 - 14.8)	7	6.3 (2.6 - 12. 6)
North	27	2	7.4 (0.9 - 24.3)	2	7.4 (0.9 - 24.3)
Northeast	47	4	8.5 (2.4 - 20.4)	3	6.4 (1.3 - 17.5)
South	7	2	28.6 (3.7 - 71.0)	1	14.3 (0.4 - 57.9)
Total	529	46	8.7 (6.4 - 11.4)	41	7.8 (5.6 -10.4)

* compare prevalence of HBV or HCV infection between Bangkok versus provincial areas: chi-square = 2.48, p value = 0.115

Table 3. Factors to predict HBV and HCV co-infection with HIV in Thai HIV-infected patients

Factors	No co-infection (n=444) number (%)	HBV co-infection (n=46) number (%)	p value	HCV co-infection (n=41) number (%)	p value
Gender					
Male	236 (53.2)	30 (65.2)	0.118	32 (78.1)	0.002
Female	208 (46.8)	16 (34.78)		9 (21.9)	
Age, mean ± SD	36.6 ± 8.7	39.8 ± 9.6	0.019	35.4 ± 8.5	0.398
Residential area					
Bangkok	256 (57.7)	29 (63.1)	0.481	28 (68.3)	0.186
Provincial areas	188 (42.3)	17 (36.9)		13 (31.7)	
Sexual preference					
Homosexual	10 (1.9)	0	1.000	0	1.000
Heterosexual	519 (98.1)	46 (100)		41 (100)	
Intravenous drug use					
Yes	0	4 (8.7)	<0.001	30 (73.2)	<0.001
No	444 (100)	43 (93.5)		14 (34.1)	
History of jaundice					
Yes	36 (8.1)	3 (6.5)	0.705	0	0.058
No	408 (91.9)	43 (93.5)		41 (100)	
History of receiving blood transfusion					
Yes	20 (4.5)	3 (6.5)	0.538	2 (4.9)	0.912
No	424 (95.5)	43 (93.5)		39 (95.1)	
History of AIDS defining illness					
Yes	125 (28.2)	14 (30.4)	0.744	15 (36.6)	0.254
No	319 (71.8)	32 (69.6)		26 (63.4)	
On antiretroviral therapy					
Yes	350 (78.8)	38 (82.6)	0.548	27 (65.8)	0.056
No	94 (21.2)	8 (17.4)		14 (34.2)	
Serum alanine transaminase, median (range)	41 (11-246)	43 (25-197)	0.139	56 (25-249)	0.003
CD4 cell count, median (range)	194.5 (2-1161)	177.5 (11-528)	0.187	161 (4-887)	0.345

range = 2-1161 cells/mm^3) but these differences were not statistically significant (p = 0.345).

The substudy of the prevalence in patients with and without IVDU showed that the prevalence of HBV co-infection was 11.8% (95% CI: 8.4%, 13.2%) in patients with IVDU and 8.5% (95% CI: 6.1%, 10.8%) in patients without IVDU (p = 0.04). The prevalence of HCV co-infection with HIV was 88.2% (95% CI: 76.2%, 92.4%) in patients with IVDU and 2.8% (95% CI: 1.4%, 3.4%) in patients without IVDU (p < 0.001).

Discussion

The present study found that the prevalence of HBV or HCV co-infection with HIV were about 9% and 8% in HIV-infected patients. Since the study site was a tertiary care hospital, nearly half of the patients were referred from every part of Thailand and allowed us to determine the prevalence outside Bangkok. The prevalence of HBV or HCV co-infection with HIV in Bangkok and provincial areas were not different. The prevalence of HBV infection in HIV-infected patients from the present study was within the range of the prevalence of HBV infection in the general Thai population and Asian population from previous studies (3% to 10%)[20-23].

On the other hand, the prevalence of HCV co-infection was much higher than previous reports which was 0.98% to 2.9% in the general Thai population[24,25] but not as high as in HIV-infected patients in the United States and European countries, 15% to 30%[1,4,15-19]. The authors also found that intravenous drug use was a common risk factor for either HBV or HCV co-infection although this factor was a minority population of HIV-infected patients in Thailand[26]. Age of patients with HBCV co-infection was significantly higher than the other two groups. This finding was concordant with previous studies, which reported that higher age was associated with a higher risk to HBV infection[20-22,24,27]

In addition to a history of intravenous drug use, male gender ($p = 0.002$) and elevated serum alanine transaminase ($p = 0.003$) were associated with HCV co-infection. The factor of male gender can be explained from the natural feature of intravenous drug users in Thailand, in that 94% were male[28]. Regarding elevated serum alanine transaminase, a previous study also showed that HCV co-infection with HIV had a significantly higher serum alanine transaminase[29]. Accordingly, in addition to a history of intravenous drug use, an elevated serum alanine transaminase may be another factor to predict HCV co-infection. This would be useful for clinical practice in a setting of limited resources where anti-HCV cannot be routinely tested in all HIV-infected patients.

The results from the present study showed that other clinical factors including history of jaundice, receiving blood transfusion, AIDS defining illness, antiretroviral therapy, and CD4 cell count were not associated with HBV or HCV co-infection with HIV. Sexual preference that was not associated with HBV or HCV co-infection in the present study may be due to a very small population of homosexual participants in the present study and general population of HIV-infected patients in Thailand. However, in a number of studies including a substantial proportion of homosexual participants showed that homosexuality was not associated with HBV or HCV co-infection[4,6,17].

The results of the authors substudy of prevalence in patients with and without IVDU demonstrated that the prevalence of both HBV and HCV co-infection with HIV was higher in IVDU patients. This confirms that IVDU is an important factor associated with both HBV and HCV co-infection with HIV. In addition, the prevalence of HCV co-infection with HIV was much higher in patients with IVDU. This finding is concordant with the previous studies that the prevalence of HCV co-infection in Thai HIV-infected patients with IVDU is very high[30-32].

The present study has some limitations. It is a cross-sectional study and cannot establish a causal relationship between the time of exposure and subsequent infection. The study was conducted in a hospital setting, not a community setting. However, the results can be implied to approximate and prepare for clinical care of HIV-infected patients. HCV RNA testing can be used to screen for HCV infection but the cost of testing is prohibitive particularly in the resources-limited setting. Immunosuppression from HIV infection may impair antibody formation, and false-negative HCV antibody tests have been reported in individuals co-infected with HIV[33,34]. However, these cases were reported before the availability of the third-generation assay for anti-HCV. High sensitivity up to 97% has been achieved with third-generation assay [35]. In addition, a study of HCV screening conducted in 559 HIV-infected patients and 944 non-HIV-infected patients indicates that HIV infection does not alter the approach to HCV screening, which should be performed with third-generation assays for anti-HCV unless acute infection is suspected[36].

In conclusion, the prevalence of HBV and HCV co-infection with HIV in Thailand is in a significant rate. History of intravenous drug use is a major risk factor of both HBV and HCV co-infection. Male gender and elevated serum alanine transaminase level may predict the higher risk for HCV co-infection. Further investigations to evaluate the cost-effectiveness of routine testing or testing in selected groups of patients in a resources-limited setting should be studied.

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ความชุกของการติดเชื้อไวรัสตับอักเสบชนิดบี และไวรัสตับอักเสบชนิดซีร่วมกับเอชไอวีในผู้ป่วยไทย

สมนึก สังฆานุภาพ, อัษฎา วิภากุล, วีรวัฒน์ มโนสุทธิ, ศศิโสภิณ เกียรติบูรณกุล, กัลยาณี อตมศิริกุล, อนุชาติ อ่วมขยัน, อัมรินทร์ ทักขิญเสถียร

ที่มา *: ไวรัสตับอักเสบชนิดบี ไวรัสตับอักเสบชนิดซี และไวรัสเอชไอวี สามารถติดต่อได้โดยทางเดียวกัน การติดเชื้อไวรัสตับอักเสบชนิดบีและไวรัสตับอักเสบชนิดซีร่วมกับเอชไอวีพบว่าทำให้อัตราการมีชีวิตสั้นลง เพิ่มความเสี่ยงในการเป็นโรคตับรุนแรง และเพิ่มความเสี่ยงในการเกิดภาวะเป็นพิษจากการรักษาโดยใช้ยาต้านไวรัส ข้อมูลเกี่ยวกับความชุกของการติดเชื้อไวรัสตับอักเสบชนิดบีและไวรัสตับอักเสบชนิดซีร่วมกับเอชไอวีในประเทศไทยยังคงมีจำกัด*

วิธีวิจัย *: การศึกษาแบบตัดขวางเพื่อหาความชุกของการติดเชื้อไวรัสตับอักเสบชนิดบีและไวรัสตับอักเสบชนิดซีร่วมกับเอชไอวีในผู้ป่วยติดเชื้อเอชไอวี โดยศึกษาในผู้ป่วยติดเชื้อเอชไอวีทุกรายที่มารับการรักษาที่โรงพยาบาลรามาธิบดี ในเดือนมีนาคม 2546*

ผลการศึกษา *: มีผู้ป่วยทั้งสิ้น 529 ราย อายุเฉลี่ย 36.7 ปี ร้อยละ 56.5 เป็นเพศชาย ร้อยละ 58.8 อาศัยในกรุงเทพฯ ที่เหลือเป็นผู้ป่วยที่มาจากต่างจังหวัด ร้อยละ 98.1 ติดเชื้อเอชไอวีมาจากเพศสัมพันธ์แบบรักต่างเพศ ความชุกของการติดเชื้อไวรัสตับอักเสบชนิดบีและไวรัสตับอักเสบชนิดซีร่วมกับเอชไอวีเท่ากับร้อยละ 8.7 และร้อยละ 7.8 ตามลำดับ ไม่มีความแตกต่างของความชุกนี้ในผู้ป่วยที่อาศัยในกรุงเทพฯ และที่มาจากต่างจังหวัด ($p = 0.115$) ประวัติการใช้ยาเสพติดฉีดเข้าเส้นมีความสัมพันธ์กับการติดเชื้อไวรัสตับอักเสบชนิดบี และไวรัสตับอักเสบชนิดซี ($p < 0.001$) การติดเชื้อไวรัสตับอักเสบชนิดซียังมีความสัมพันธ์กับเพศชาย ($p = 0.002$) และระดับเอนไซม์ทรานซามิเนสที่สูง ($p = 0.0003$).*

สรุป *: ความชุกของการติดเชื้อไวรัสตับอักเสบชนิดบีและไวรัสตับอักเสบชนิดซีร่วมกับเอชไอวีในผู้ป่วยไทยมีจำนวนไม่น้อยในภาวะที่มีทรัพยากรจำกัด ประวัติการใช้ยาเสพติดฉีดเข้าเส้นเป็นตัวชี้ที่สำคัญในการตรวจคัดกรองการติดเชื้อไวรัสตับอักเสบชนิดบีและไวรัสตับอักเสบชนิดซีร่วมกับเอชไอวี เพศชาย และระดับเอนไซม์ทรานซามิเนสที่สูงช่วยชี้นำว่าผู้ป่วยอาจติดเชื้อไวรัสตับอักเสบชนิดซี*