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Factors associated with HIV and HBV co-infection in Northern Thailand

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ABSTRACT

Objective: To identify factors associated with HIV and hepatitis B virus (HBV) co-infection in Northern Thailand.
Methods: We tested 355 newly diagnosed HIV-infected subjects for hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody by using immunochromatographic and ELISA methods. Cases were positive for one or more of the HBV markers and controls were negative for all HBV markers. All study subjects were asked to complete a questionnaire to identify the associations between variables. We used logistic regression model to evaluate the associations between demographic and behavioral variables and HIV/HBV co-infection.
Results: A total of 41 cases and 83 controls were suitable to analyze in the study. Among them, 15.0% were males, 40.3% were 30–39 years old, 62.9% were married, 18.6% were illiterate and 89.5% were employed. Besides, 26 cases (23.4%) had a history of a blood transfusion, 12.9% had a history of jaundice, 29.0% had a CD4 cell count $\leqslant$ 200 cells/mm^3, 0.8% were intravenous drug user, 29.8% tattooed, 64.5% had a body piercing, 12.1% were commercial sex workers, 11.3% had first sexual intercourse at age $\leqslant$ 15 years old, 6.5% were homosexual, and no one had a history of HBV vaccination. After controlling for all possible confounder factors in the multiple logistic regression model, we found two factors associated with HIV/HBV co-infection: number of years in school and CD4 cell count. Subjects with no education were more likely to have HIV/HBV co-infection, which was 7.07 times (odds ratio = 7.07, 95% confidence interval = 1.77–28.24) greater than those with 7 years of education group. Subjects with CD4 count $\leqslant$ 200 cells/mm^3 were less likely to have HIV/HBV co-infection than those with a CD count $\geqslant$ 200 cells/mm^3 (odds ratio = 0.35, 95% confidence interval = 0.13–0.94).
Conclusions: Our findings suggest that having a good education and having a good immune status are a protective factor of HIV/HBV co-infection. A practical approach would be a provision of wide access to general and sex education on the risk and prevention of HIV, HBV, and a promotion of HBV immunization.

1. Introduction

In 2015, 30 years after HIV infection was first identified, the World Health Organization estimated that there were 70 million people worldwide living with HIV infection and 35 million had died from HIV or acquired AIDS[1].

The World Health Organization also estimated that the prevalence of hepatitis B virus (HBV) infection in Southeast Asia was 8.0%[1]. In 2014, more than 240 million people were estimated to have chronic hepatitis B infection, and more than 780 000 people died every year due to acute or chronic HBV infection[2]. The disease has a wide spectrum of manifestation ranging from being clinically asymptomatic with only serologic markers to fatality. Both HIV and hepatitis B are bloodborne infections and they both share similar risk factors and routes of transmission via sexual intercourse, intravenous drug use and vertically from mother to newborn[3]. Six months after acute infections, 10.0% of new acute HBV infection cases will develop into chronic HBV[4]. In an immunocompromised state such as with HIV/AIDS infection, the clearance of HBV after acute infection is likely to be poorer in an immunocompetent person, increasing the risk of becoming a chronic HBV carrier[5]. More than 80.0% of HIV-infected patients have markers for past or current HBV infection[6]. Inuzuka *et al.*[7] reported that 8.0%–11.0% of hepatitis B infection persons became a carrier. The mortality rate of HIV/HBV co-infection from chronic hepatitis is increased beyond that of either infection alone[8].

In Thailand, from the first HIV/AIDS report in 1984 to September 2012, there had been 276 947 cumulative number of cases with

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The study protocol was performed according to the Helsinki declaration and approved by the Committee for the Protection of Human Subject of Mae Fah Luang University, Thailand, No.22/2554. Informed written consent was obtained from the subjects and the director of hospitals.

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sexual intercourse being the major route of transmission[9]. Chiang Rai Province in Northern Thailand has the highest HIV/AIDS prevalence of HIV infection[10]. The total number of HIV/AIDS patients from 1988 to October 2012 reported from Chiang Rai Provincial Public Health Office was 34 352 with 15 402 deaths[11].

Otto-Knappa *et al.*[8] reported HIV infection accelerates the progression of hepatitis C virus and HBV liver disease by increasing HBV loads and shorting the time of the onset of cirrhosis. Chronic hepatitis is an important cause of hospitalization and mortality among HIV-infected patients receiving highly active antiretroviral therapy (HAART) in developed countries[12]. With the use of HAART, liver disease has emerged as a major cause of death among HIV-infected persons[13,14].

This study investigated the factors associated with HIV/HBV co-infection in Northern Thailand which is an endemic area for both infections.

2. Materials and methods

2.1. Study design

We conducted a case-control study design among a hospital-based population who were recently diagnosed with HIV. Cases were patients with HIV/HBV co-infection and HBV infection was confirmed by having one or more positive tests for HBV serology. Controls were those with all negative tests for HBV. Statistical comparisons were made between cases and controls to identify factors associated with HIV/HBV co-infection.

2.2. Study sites and study samples

We randomly selected 9 out of 18 hospitals in the Chiang Rai Province. The sites were in districts of Mae Chan, Mae Sai, Chiang Saen, Khun Tan, Phaya Meng Rai, Theong, Mae Suai, Mae Lao and Phan.

The study samples were patients who were first diagnosed with HIV positive during 2010–2012 aged over 18. They had lived in Chiang Rai Province for at least 2 years before the commencement of the study, and had visited at least once in the selected anti-retroviral (ARV) clinics.

2.3. Sample size estimation

The sample size was calculated by using an alpha at 5.0% and 80.0% for the power of the test. The calculation yielded a figure of 120 cases plus 10.0% to account for loss to follow up resulting in a final count of 132 cases and 132 controls. All participants knew they were HIV-positive, and gave informed consent prior to participating in the study. Both cases and controls were selected from the lists of HIV patients from the target hospitals by purposive selecting technique. Only those who had met criteria were recruited into the study.

2.4. Research instruments

All participants were asked to fill out a structured questionnaire asking about socio-demographic characteristics, medical history, risk behaviors and sexual behaviors.

Socio-demographics were age, gender, marital status, religion, area of residence, number of family members, education level, occupation, monthly income, and debt. Medical history asked about history of blood transfusion, hemodialysis, jaundice, HBV vaccination, use of ARV drugs, recent CD4 cell count, length of HIV infection and presence of any comorbidities. Subjects were asked about living with HBV-infected member in the same family, sharing personal objects with family members, history of intra drug use, history of drug abuse throwing[through?] inhalation or orally, tattooing, piercing, alcohol use, and smoking. Subjects were also asked about ages at first sexual intercourse, sexual orientation, history of sexual transmitted diseases, history of commercial sex work, number of sexual partners, history of oral and anal sex of the use of condoms.

The validity of questionnaire was validated by three external experts before used. It was adjusted if the score was less than 0.5 in the Item Objective Congruence Index method. The reliability of the questionnaire was tested among 15 patients with test-retest reliability method before use in the field with a Cronbach's alpha of 0.81.

2.5. Laboratory methods

Five milliliters of venous blood was obtained from each subject and the hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) were examined (Figure 1). HBsAg was detected by immunochromatography Determine® or AleraTM with 99.9% specificity and 95.2% sensitivity; anti-HBs by NanoSign Anti-HBs immunochromatography with greater than 99.0% specificity and sensitivity; Enzyme immunoassay MonolisaTM Anti-HBc Plus was used for anti-HBc detection with greater than 99.8% specificity and 100.0% sensitivity.

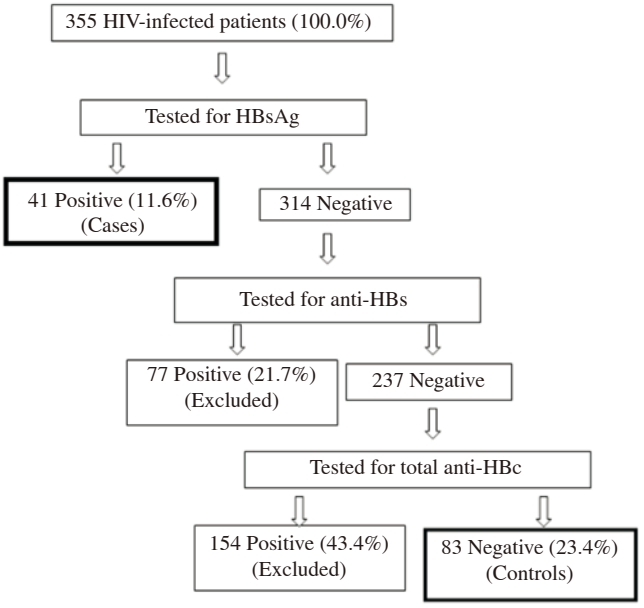

Figure 1. Selection of cases and controls.

2.6. Statistical analysis

Data were double-entered and validated by using Microsoft Excel. Data analysis was carried out by using SPSS version 11.5, 2006 (SPSS, Chicago, IL) and Epi-Info version 6.04d (US Centers for Disease Control and Prevention, Atlanta, GA).

Descriptive statistics (means, standard deviations, frequencies, and percentages) were used to describe the general characteristics of the participants.

Univariate analysis was then used to identify factors associated with HIV/HBV co-infection at $\alpha = 0.10$. All significant variables were included in the model for multivariate analysis.

Multiple logistic regression analysis was conducted to identify factors associated with HIV/HBV co-infection by controlling all possible confounding factors. Variables that remained associated

with HIV/HBV co-infection at α = 0.05 in the statistical model were considered significantly associated with HIV/HBV co-infection.

2.7. Ethical considerations

This study was approved by the Ethics in Human Research Committee of Mae Fah Luang University (No. 22/2554). Permission of performing the study was also obtained from the Provincial Chief of Public Health Office for Chiang Rai.

3. Results

A total of 355 cases of HIV-infected patients were recruited into the study. Among them, 41 (11.6%) were positive for the HBsAg and assigned as cases group, while 314 with negative HBsAg were tested for anti-HBs of whom 77 (21.7%) were positive and were excluded from the study. The remaining 237 were retested for total anti-HBc and excluded if they were positive. Finally, 83 (23.4%) were negative for all HBV markers and assigned as control group.

Among the total of 124 cases, 62 cases (50.0%) were males, 40.3% were aged from 30 to 39 years old, 62.9% were married, 95.9% were Buddhism, 76.7% had a family member ⩽ 4 persons, 18.6% were illiterate, and 89.5% were employed.

The statistical significant differences of general characteristics between those who were included and those who were excluded were in their marital status ($P = 0.031$) and occupation ($P = 0.001$).

It was found in the simple logistic regression model with a significant level of α at 0.10 that three factors had shown a statistical significant association with HIV/HBV co-infection. They were years in school, CD4 cell count and the length of HIV infection. Among those who had no education, the risk of co-infection was 5.89 times [odds ratio (OR) = 5.85, 90% confidence interval (*CI*) = 2.12–16.14] higher than those who had 7 years of education. CD4 ⩽ 200 cells/mm^3 (OR = 0.35, 90% *CI* = 0.16–0.77) appeared to have a lower risk of co-infection while the length of HIV infection ⩽ 3 years (OR = 2.44, 90% *CI* = 1.19–5.04) group showed a higher risk than controls (Table 1).

Table 1

Univariate analysis of factors associated with HIV/HBV co-infection.

Factors	Case		Control		OR	90% *CI*
	n	%	*n*	%		
Total	41	100.0	83	100.0		
Sex						
Male	21	51.2	41	49.4	1.08	0.57–2.02
Female	20	48.8	42	50.6	1.00	
Age (years)						
⩽ 29	3	7.3	8	9.6	1.00	
30–39	16	39.0	34	41.9	1.26	0.37–4.25
40–49	12	29.3	31	37.4	1.03	0.30–3.59
⩾ 50	10	24.4	10	12.1	2.67	0.70–10.13
Marital status						
Married	29	70.7	49	59.01	1.97	0.63–6.23
Divorced/widowed	9	21.9	24	28.91	1.25	0.36–4.40
Single	3	7.4	10	12.05	1.00	
Religion						
Christian	2	4.9	3	3.6	1.37	0.29–6.35
Buddhism	39	95.1	80	96.4	1.00	
Number of family member (persons)						
⩽ 4	31	75.6	64	77.1	1.00	
⩾ 5	10	24.4	19	22.9	1.09	0.52–2.27
Years in school						
No education	13	31.7	10	12.1	5.85	2.12–16.14*
⩽ 6	22	53.7	46	55.4	2.15	0.91–5.07
⩾ 7	6	14.6	27	32.5	1.00	
Occupation						
Unemployed	5	12.2	8	9.6	1.30	0.48–3.52
Employed	36	87.8	75	90.4	1.00	
History of blood transfusion						
Yes	11	26.8	18	21.7	1.32	0.64–2.74
No	30	73.2	65	78.3	1.00	
History of jaundice						
Yes	6	14.6	10	12.1	1.25	0.50–3.12
No	35	85.4	73	87.9	1.00	
ARV drug						
Yes	37	90.2	79	95.2	1.00	
No	4	9.8	4	4.8	2.14	0.64–7.15
Comorbidity						
Yes	11	26.8	19	22.9	1.24	0.60–2.54
No	30	73.2	64	77.1	1.00	
CD4 cell count (cells/mm^3)						
⩽ 200	7	18.9	29	40.3	0.35	0.16–0.77*
⩾ 201	30	81.1	43	59.7	1.00	
Length of HIV infection (years)						
⩽ 3	32	78.1	48	59.3	2.44	1.19–5.04*
> 3	9	21.9	33	40.7	1.00	
Living with HBV-infected patient in family						
Yes	3	7.3	3	3.6	2.11	0.53–8.38
No	38	92.7	80	96.4	1.00	
Sharing personal objects in family						
Yes	5	12.2	11	13.3	0.91	0.35–2.35
No	36	87.8	72	86.7	1.00	
History of tattooing						
Yes	11	26.8	26	31.3	0.80	0.40–1.61
No	30	73.2	57	68.7	1.00	
History of piercing						
Yes	28	68.3	52	62.7	1.28	0.66–2.50
No	13	31.7	31	37.3	1.00	
Alcohol drinking (before knowing HIV status)						
Yes	35	85.4	68	81.9	1.29	0.54–3.06
No	6	14.6	15	18.1	1.00	
Smoking (before knowing HIV status)						
Yes	20	48.8	34	41.9	1.37	0.73–2.58
No	21	51.2	49	59.1	1.00	
History of being commercial sex worker						
Yes	6	14.6	9	10.8	1.41	0.56–3.57
No	35	85.4	74	89.2	1.00	
Age at first sexual intercourse (years)						
⩽ 15	7	17.5	7	8.4	1.00	
> 15	33	82.5	76	91.6	0.43	0.17–1.12
History of STDs						
Yes	27	65.9	58	69.9	0.83	0.43–1.62
No	14	34.1	25	30.1	1.00	
History of being homosexual						
Yes	4	9.8	4	4.8	2.14	0.64–7.15
No	37	90.2	79	95.2	1.00	
Oral sex						
Yes	7	17.1	18	21.7	0.74	0.33–1.67
No	34	82.9	65	78.3	1.00	
Anal sex						
Yes	3	7.3	3	3.6	2.11	0.53–8.38
No	38	92.7	80	96.4	1.00	
Number of partners						
1	5	12.2	10	12.1	1.00	
2–9	19	46.3	43	51.8	0.88	0.32–2.42
⩾ 10	17	41.4	30	36.1	1.13	0.41–3.18

*: Significant level at α = 0.10.

Using multiple logistic analysis model at a significant α level of 0.05, after controlling for all possible confounding factors, we found that two variables had statistically significant association with HIV/HBV co-infection. People who had no education were at 7 times greater association of HIV/HBV co-infection (95% *CI,* 1.77–28.24) than those having seven or more years in school. Subjects who had CD4 cell count of ⩽ 200 cells/mm^3 had a lower risk of HIV/HBV co-infection as compared to those with ⩾ 201 cells/mm^3 (OR = 0.35, 95% *CI* = 0.13–0.94) (Table 2).

Table 2
Multivariate analysis of factors association with HIV/HBV co-infection.

Factors	OR	95% *CI*
Years in school		
No education	7.07	1.77–28.24*
1–6	2.21	0.72–6.76
⩾ 7	1.00	
CD4 cell count (cells/cm^3)		
⩽ 200	0.35	0.13–0.94*
⩾ 201	1.00	

*: Significant level at α = 0.05.

4. Discussion

In total, 355 HIV-infected patients participated in this study; 41 of HIV/HBV co-infection were cases and 83 non-HBV infected were controls. In the final statistical model, it was found that education and CD4 level had statistically significant associations with HIV/HBV co-infection.

In the analysis of some variables, they were found to be statistically significant in univariate but not in multiple logistic regression. This may be due to our limitation of the power of the test since some categories had very few cases particularly in the control group. Also, we set the alpha levels differently at 0.10 for univariate and 0.05 for multivariate analysis.

Another confounding factor may be due to the high HBV prevalence in most Asian countries[15]. Thailand started to routinely immunize infants against HBV in 1992[16]. However, all of our subjects had not had hepatitis B vaccination.

More than half of the subjects in our study were males. However, Kouassi-M'Bengue *et al.*[6] presented that female was the main group of HIV/HBV co-infection. Miailhes *et al.*[17] and Balewa *et al.*[18] reported that the absence of HBsAg (but not HBe) markers was related to age, number of partners, length of HBV therapy, in co-infection. In some instances, HBsAg re-appeared after the withdrawal of anti-HBV treatment. In this study, no subject was on anti-HBV treatment. Firnhaber *et al.*[19] reported that 5.4% of HBV DNA was detectable where surface antigen was negative. However, the phenomenon was not statistically significant.

Audsley *et al.*[20] found that the frequency of HIV mutation differed between the HBV co-infected and mono-infected of the same genotype and co-infection has a significant impact on the natural progression of the HBV-related liver diseases. Our studies did not study the mutation nor identify the liver diseases.

This study found HIV-infected patients with a CD4 cell count of ⩾ 201 cells/mm^3 had a greater association with HIV/HBV co-infection with a statistical significance while compared to those who had CD4 ⩽ 200 cells/mm^3. This might be due to those subjects who had a CD4 ⩽ 200 cells/mm^3 had to meet more often with health personnel and getting more opportunity to be suggested for living in a healthy behaviors. Therefore, it made less the opportunity to get infection of HBV. Moreover, it could be the impact of losing amount of CD4 after getting HIV infection. Therefore, HBV infections in later may not completely produce individual immune response. However, the mean of CD4 cell count in cases was higher than in controls (308.70 cells/mm^3 *vs.* 255.97 cells/mm^3), which was not statistically significant. This finding did not correspond to the study by Sungkanuparph *et al.*[21] in Thailand, where they found the median serum CD4 cell count of HIV/HBV co-infection groups was lower than the non-co-infected (HIV-infected only) group, but the difference was not statistically significant. A study of HIV/HBV co-infected patients in India found that HBV genotypes A, C, and D were related to CD4 cell count of less than 200 cells/mm^3. However, Hoffmann gave a strong conclusion that the consequences of co-infection included increased liver-related morbidity and mortality increased HBV replication, and immune reconstitution of HBV[15]. In the setting of HAART with its hepatotoxicity from ARV drugs, the issue of understanding the role of HBV co-infection is especially important in the region where antiretroviral program is expanding which includes Northern Thailand. Moreover, lacking of HAART among the HIV/AIDS patients could introduce for loss of anti-HBsAg since the CD4 which has a major role for immune response had been loosen from HIV infection[22-26]. This could be a confounding factor in our study.

In this study, participants who had no education were at a significantly greater association with HIV/HBV co-infection. Mehmet *et al.*[27] found that education level had a statistically significant effect on HBV seropositivity in urban areas. They suggested that the use of health facilities increased with the education level. In addition, a study by Stover *et al.*[28] found that a lower level of education (less than high school) was associated with HBV infection in both HIV-infected and HIV-uninfected but high-risk women.

Provision essential knowledge of HIV and HBV and their risk factors for those susceptible populations in Thailand is needed in Thailand. Encouraging Thai people to access educational system is important to reduce the new case of HIV/HBV co-infection. However, in the point of lower CD4 presented as a preventive factor of HIV/HBV co-infection, we suggest to investigate more about this association by using a stronger study design.

Conflict of interest statement

We declare that we have no conflict of interest.

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