Risk Factors of HIV and HBV Co-infection in Northern Thailand

Tawatchai Apidechkul, Dr.P.H. (Epidemiology)*, Sauwaluck Pongwiriyakul, M.Sc., Mitra Cassely, M.D.*, Chomnard Pojanamart, Ph.D.*****

**School of Health Science, Mae Fah Luang University, **Scientific and Technological Instrument Center, Mae Fah Luang University, ***School of Nursing, Mae Fah Luang University, Chiang Rai 57110, Thailand.*

ABSTRACT

Objective: To identify the risk factors of HIV/ HBV coinfection among HIV persons.
Methods: 356 newly diagnosed HIV positive patients had their blood tested for HBV serological markers: HBsAg, HBsAb and HBcAb by immunochromatographic and ELISA methods. Cases were those positive for one or more of the HBV markers, and controls were negative for all HBV markers. All completed questionnaires designed to identify risk factors. Logistic regression statistical method was used to find the associations between demographic and behavioural parameters and the coinfection status.
Results: A total of 122 out of 356 cases were suitable for analysis. Fifty percent were male, 40.3% were aged 30-39 years old, 62.9% were married, 18.6% were illiterate, and 10.5% were unemployed. After controlling for possible confounding factors the multiple logistic regression identified two factors associated with HIV/HBV co-infection namely number of years in school and CD4 cell count. The "no education" group had a greater risk of 7.07 times (OR=7.07, 95% CI=1.77-28.24) than the "≥13 years" group. CD4 "≤ 200 cells/mm^3" was a protective factor protect for HIV and HBV coinfection when compared to "≥ 200 cells/mm^3" group (OR=0.35, 95% CI=0.13-0.94).
Conclusion: The study suggests that a good education may reduce HIV/HBV co-infection. A practical approach would be a provision of wide accessibility to quality general and sex education on the risk and prevention of HIV, HBV, and a promotion of HBV immunization.

Keywords: HBV-HIV Co-infection, risk factors, CD4, Thailand

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INTRODUCTION

A coinfection of HIV and HBV has become a major public health problem after emer gence of the human immunodeficiency virus. In 2013, thirty years after HIV infection was first identified, the World Health Organization (WHO) reported that 70 million people worldwide had been infected and 35 million had died of AIDS[1], whereas hepatitis B virus infection is one of dominating causes of human morbidity and mortality. Hepatitis B prevalence is as high as 8.0% in South East Asia[2]. In 2014, more than 240 million people had chronic forms of the disease, and more than 780,000 people die every year due to acute or chronic hepatitis B1. More than 80.0% of HIV-infected patients show some markers of past or current HBV infection[3], and 8.0-11.0% of them are found to be hepatitis B carriers.[4] HIV/HBV co-infection mortality rate from chronic hepatitis is increased beyond that of either infection alone[5].

Correspondence to: Tawatchai Apidechkul
E-mail: tk2516ms@gmail.com, tawatchai.api@mfu.ac.th

In Thailand, from the first HIV/AIDS report in 1984 to September 2012, there had been 276,947 cumulative number of cases of HIV/AIDS.[6] Chiang Rai province in the northernmost part has the highest HIV/AIDS incidence in the country.[7] The cumulative number of HIV/AIDS patients in Chiang Rai province from 1988 to October 2012 was 34,352 and 15,402 had died[8]. HIV itself accelerates the progression of HCV and HBV liver disease by increasing hepatitis B viral loads and shortly stimulates the onset of cirrhosis.[5] Chronic viral infections of the liver have been one of the most important causes of hospitalization and mortality among HIV-infected patients during the highly active antiretroviral therapy (HAART) era in developed countries.[9] During the treatment period with HAART, liver failure has emerged as a major cause of death in HIV-infected persons.[10,11] This study aimed to investigate the risk factors of HIV/HBV co-infection particularly in the high epidemic area of both infections in northern Thailand.

MATERIALS AND METHODS

Study design

A case-control study design was conducted in a hospital-based population of recently diagnosed adult HIV-positive patients. Cases were patients with hepatitis B coinfection which was identified by showing one or more positive tests for HBV serology. Controls were negative for HBV tests. Statistical comparisons were made between cases and controls in an attempt to identify characteristics of each group that may indicate risk or protective factors.

Study sites and study sample

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 sample were patients who were first diagnosed HIV positive during 2010-2012, aged over 18, 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 ARV clinics.

Sample size estimation

The sample size was calculated using alpha between 5.0% and 80.0% as power of the test. The formulaic calculation yielded a figure of 120 cases, 120 controls, plus 10.0% to compensate for any loss making a final 132 cases and 132 controls.

All participants knew they were HIV positive. They gave informed consent to participate in the study. They had lived in Chiang Rai province for at least two years at the time of interview. They were aged over 18.

Cases were defined as having at least a positive HBsAg. Control was negative for HBsAg, Anti-HBs, and Anti-HBc.

Research instruments

Two instruments were used: a structured questionnaire, and blood test for HBV markers. The four parts questionnaire consisted of socio-demographic characteristics, medical history, risk behavior, and sexual behavior.

Socio-demographic data were recorded: age, gender, marital status, religion, area of residence, number of family members, education, occupation, monthly income, and debt. Medical history asked about history of blood transfusion, hemodialysis, jaundice, HBV vaccination, use of antiretroviral (ARV) drug, recent cluster of differential 4 (CD4) cell count, length of HIV infection, and comorbidity. Risk behavior asked about experience in living with HBV-infected member in the same family, sharing personal objects with family members, history of intra-venous drug user (IDU), history of drug abuse by inhalation and oral route, tattooing, piercing, alcohol drinking, and smoking. Sexual risk behavior experience included age at first sexual intercourse, sexual orientation, history of sexual transmission diseases (STDs), history of commercial sex work, number of partners, history of oral and anal sex, and use of condoms.

The validity of the questionnaire was done by three external experts before use. Questions were adjusted and corrected if the item objective congruence index (IOC) score was below 0.5. The reliability of the questionnaire was tested in 15 patients by test-retest reliability method before use in the field with Cronbach's alpha 0.81.

Laboratory methods

For HBV status 5 ml of venous blood was obtained from each subject for HBsAg, anti-HBs, and anti-HBc.

HBsAg was detected by immunochromatography Determine® or Alera™; anti-HBs by NanoSign Anti-HBs immunochromatography; and Enzyme immunoassay Monolisa™ Anti-HBc Plus was used for anti-HBc detection.

Data collection

Ethical consideration and data collection were approved by the relevant ethics committees and hospital ARV clinics. Clinic staff was fully informed and their willingness to cooperate was confirmed. The selection of cases for recruitment was selected from clinic lists and their computerized records. Inclusion and exclusion criteria were applied and suitable cases were chosen for the next stage which was a face to face interview and blood test. Chosen patients were invited to attend when an informed consent was obtained. A thirty-minute interview was conducted by one of two trained interviewers who was of the same sex as the patient in a room with maximum privacy. The information and data collected were securely stored.

Five ml of venous blood was obtained. Serum was separated, labeled by coding and transported to the laboratory. Serum was stored at -20°C if not immediately tested at the lab. Fig 1 shows the hierarchy of testing for HBV markers.

Statistical analysis

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

Descriptive statistics (means, standard deviation, frequency, and percentage) were used to describe the general characteristics of the participants.

Univariate analysis was then used to identify risk factors associated with the HIV/HBV co-infection at α=0.10. All significant variables were considered and maintained in the model for multivariate analysis.

Multiple logistic regression analysis was conducted to identify the risk factors associated with the 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 determined as the risk factors.

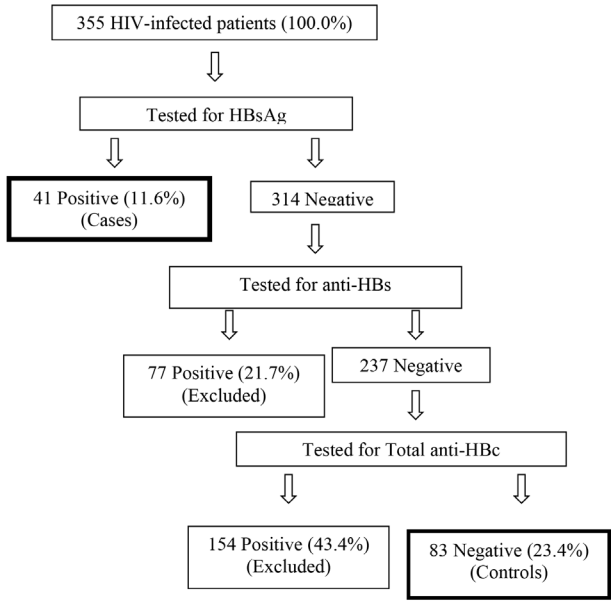

Fig 1. Process of identifying case and control.

Ethical consideration

This study was approved by the Ethics in Human Research Committee of Mae Fah Luang University (No. 22/2554). A permission to collect the data in 9 hospitals in Chiang Rai province was granted by the Provincial Chief of Public Health Office. All subjects who had been found with HBV infection had been suggested to meet a medical doctor to receive an appropriate treatment.

RESULTS

Three hundred and fifty cases of HIV-infected patients were recruited into the study. Cases: Forty one (11.6%) were positive for the HBsAg and assigned as case group. Controls: 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 re-tested for total anti-HBc and excluded if positive. Finally 83 (23.4%) were negative for all HBV markers and assigned as control group.

General characteristics

Out of all 355 cases; 50.4% were males and 49.6% were females. The two largest age groups were 40-49-year-old (40.2%) and 30-39-year-old (36.5%). Three hundred and thirty three cases (95.5%) were Buddhist, 54.4% were married, 56.4% had education in school between 1 and 6 years, 23.2% had no education, 44.5% worked for daily wages, 47.4% had an income ≥5,000 baht /month, and 55.8% had no debt (Table 1).

Among the case group it was found that 51.2% were males, 39.0% were aged 30-39 years old, 70.7% were married, and 95.1% were Buddhist. In the control group it was found that 50.6% were females, 41.9% were aged 30-39 years old, 59.01% were married, and 96.4% were Buddhist.

Medical history

Twenty four point five percent had a history of blood transfusion, and the average number of units of blood received was 2.4 units, 11.8% had a history of jaundice, 93.5% had received ARV drug, 97.5% had not received HBV vaccine, 30.4% had comorbidity, 34.1% had CD4 ≤200, and 74.1% had known their HIV status less than 3 years.

Only 2.5% had lived together with an HBV-infected persons in their family, and 12.7% had shared personal objects with other members of their families. Seven cases (1.9%) were IDUs, 32.1% were tattooed, 60.0% had piercing, 85.9% consumed alcohol, and 44.8% smoked.

Fifty six cases (15.8%) had a history of being commercial sex workers, with an average working period of 4.8 years, the longest of which was 26 years. Forty-nine cases (13.9%) had their first sexual intercourse at ≤15 years of age, and 59.1% had a history of STDs. Twenty-six cases (7.3%) were homosexual and 89.3% had 2 or more sex partners,18.3% had oral sex, 6.8% had anal sex, 46.8% had between 2-9 partners, and 42.5% had 10 or more partners.

Laboratory results

231 (65.1%) subjects were excluded from the control group because they had markers of past HBV infection even though they were negative for HBsAg. Only 41 cases and 83 controls were suitable for logistic regression model to identify risk factors of HIV/HBV co-infection.

The statistically 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).

In the univariate model with a significance level of α od 0.10 it was found that three factors had a statistically 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 (OR=5.85, 90% 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).

Using multiple logistic analysis model at a significant α level of 0.05, after controlling all possible confounding factors, we found that two variables had statistically significant association with HIV/HBV co-infection; which were people who had no education, were at 7 times greater risk of HIV/HBV co-infection (95%CI=1.77-28.24) than those having seven or more years in school, and cases who had CD4 cell count of ≤ 200 cells/mm3 had a lower risk of HIV/HBV co-infection compared to those with ≥201 cells/mm^3 (OR=0.35, 95%CI=0.13-0.94) (Table 2).

DISCUSSION

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

Only marital status and occupation were shown to be of statistical significance between the co-infected group and the non HBV group.

The major limitation of this study was the limited number of case and control patients included into the analysis which did not reach

TABLE 1. Univariate analysis of risk factors of HIV/HBV co-infection.

Risk factors	Case		Control		OR	90%CI
	N	%	N	%		
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	0.17-1.12
>15	33	82.5	76	91.6	0.43	
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

the number required from the earlier estimation due to very rare control group even though we did data collection for the previous three years. However, we were concerned about the recall bias which might have significantly impacted upon the analysis, so we could not extend the

TABLE 2. Multivariate analysis of risk factors in HIV/HBV co-infection.

Risk factors	OR_{adj}	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

time for data collection more than 3 years. In the analysis some variables were found to be statistically significant in univariate, but not in multiple logistic regression. This may be due to limited number of subjects and 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.[2] Thailand started to routinely immunize infants against HBV in 1992 and most of our subjects had not had the protection of HB vaccination.[12] Increase of age had a greater proportion of cases, which indicated that younger people who had been immunized by hepatitis vaccine, consequently had reduced risk of getting HBV infection.

The results of this study found the same proportion of HIV-HBV coinfection rate between sex. However Kouassi et al[13] presented that female was the main group of HIV- HBV co-infection. Miailhes et al[14] and Melashu et al[15] reported that the absence of HBsAg (but not HBe) markers was related to age, number of partners, length of HBV therapy, and coinfection. 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[16] reported that 5.4% of HBV DNA was detectable where surface antigen was negative, although the phenomenon was not statistically significant.

Jennifer et al[17] 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 hepatitis B virus related liver diseases. Our series 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 risk of HIV/HBV co-infection with a statistical significance. The mean of CD4 cell count in cases was higher than in controls (308.70 vs. 255.97 cells/mm^3), but not statistically significant. This might be because those subjects who had a CD4 ≤200 cells/mm^3 had to meet more often with health personnel and so they got more opportunity to be suggested about living with healthy behaviors, so it made less opportunity for them to get infection by HBV. Moreover, it could be the impact of losing amount of CD4 after getting HIV infection, therefore, HBV infections later may not completely produce individual immune responses. This finding did not correspond to the study by Sungkanuparph et al[18] 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, Christopher in 20102 gave a strong conclusion that the consequences of co-infection included increased liver-related morbidity and mortality, increased hepatitis B virus replication, and immune reconstitution of HBV. 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 the antiretroviral program is expanding which includes northern Thailand.

In this study, participants who had no education were at a significantly greater risk for HIV/HBV co-infection. Dursun et al in 2005[19] 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 in 2003[20] 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 of 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 cases of HIV and HBV co-infection. However, in the point of lower CD4 cell count which presented a preventive factor of HIV/HBV co-infection, we suggest to investigate more about this association by using a stronger study design.

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