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HIV and Hepatitis B Co-infection Among Perinatally HIV-infected Thai Adolescents

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Abstract

Objectives—The study aimed to determine prevalence of hepatitis B virus (HBV) co-infection and HBV antibody in perinatally HIV-infected adolescents. A secondary objective was to describe the clinical characteristics of adolescents with chronic HBV- and HIV co-infection.

Design—A multi-center cross sectional study of HIV-infected adolescents aged between 12–25 years

Methods—Hepatitis B surface antigen (HBsAg), surface antibody(anti-HBs) and core antibody(anti-HBc) were measured. Co-infection was defined as having persistent positive HBsAg. Seroprotective antibody from immunization was defined as having anti-HBs > 10 mIU/mL with negative anti-HBc.

HBV DNA, and rtM204V/I mutation analysis (lamivudine resistance associated mutation) was performed in adolescents with chronic HBV infection.

Results—From November 2010 to March 2011, 521 patients were enrolled. Mean (SD) of CD4 lymphocyte count was 685(324) cells/ μ L. Prevalence of HBV/HIV co-infected was 3.3%; 95% CI: 1.9% to 5.2 %. Protective antibody against HBV was found in 18% of population, and this was significant higher among adolescents who received hepatitis B revaccination after receiving antiretroviral therapy (93% vs. 6%, $p < 0.01$). Among adolescents with chronic HBV infection, 88% have received lamivudine; however 69% have HBV DNA > 10^5 copies/ml, and 75% had the rtM204V/I mutation.

Conclusions—The prevalence of HBV co-infection in HIV-infected Thai adolescents was 3.3%. Majority of HIV-infected adolescents had no HBV protective antibody; therefore revaccination with HBV vaccine is encouraged. A high prevalence of HBV-lamivudine resistance mutation was found, therefore HBV screening for all children prior to initiation of antiretroviral treatment should be considered to select appropriate regimen regarding both viral infections.

Keywords

HIV; adolescents; hepatitis B; co-infection

Introduction

An estimated 350 million persons worldwide are chronically infected with hepatitis B (HBV) [1]. Among HIV-infected populations, HBV is more prevalent due to overlapping transmission routes, e.g., perinatal, percutaneously contact with body fluid, and sexual exposure. The risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of HBeAg-positive mothers, to 25%-30% in infants and children under 5 years, and to less than 5% in adults [2].

HIV infection greatly affects the clinical course of hepatitis B virus infection [3]. Patients with co-infection have higher HBV DNA levels, a decreased likelihood of HBV clearance which leads to a higher chance of developing chronic HBV infection ranging from 10–15% [4], and higher rates of HBV-associated liver disease [5]. Several reverse transcriptase inhibitors, for example lamivudine and tenofovir, have activity against both HIV and HBV, making therapeutic decisions more complicated. Treating HIV infection without knowing patients' hepatitis serostatus might lead to selection of HBV-resistant mutants and vice versa [6].

The prevalence of HIV-HBV co-infection among HIV-infected adults in Thailand and in Asia is reported to be in the range of 8.7%–10% [7, 8], and 4.9% among HIV-infected children in China [9]. As of 2010, the incidence of hepatitis B infection in Thailand was only 8.4 per 10,000 persons in the population due to high coverage of immunization during childhood [10]. However, there has been no routine hepatitis B screening program among HIV-infected children in Thailand. HBV-HIV co-infection becomes an important issue when HIV-infected children become adolescents since HBV can enter a period of immune activation, and risk developing HBV drug resistance if prolonged used of lamivudine monotherapy.

This study aimed to determine the prevalence of hepatitis B virus (HBV) co-infection and protective HBV antibody in perinatally HIV-infected adolescents. The secondary objective was to describe the clinical characteristics of adolescents with chronic HBV- and HIV co-infection.

Patients and Methods

A cross-sectional study was conducted at 4 sites in Thailand, namely Research Institute for Health Sciences, Chiang Mai University (RIHES-CMU), Chiang Mai, the HIV-Netherlands-Australia-Thailand Research Collaboration (HIV-NAT), Thai Red Cross AIDS Research Centre in collaboration with Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Chiangrai Prachanukroh Hospital, Chiangrai, and Srinagarind Hospital, Khon Kean. All 4 sites participate in the Therapeutics, Research, Education and AIDS Training in Asia (TREAT Asia) Pediatric Network. Data on all children receiving HIV-related medical care at the participating sites were collected. Inclusion criteria were HIV-infected children participating in TREAT Asia Pediatric HIV Observational Database (TAPHOD) at specified sites, aged 12 years to 25 years. The study was approved by the research ethics committee of all sites. Written informed consent was obtained from adolescents or guardians at the time of enrollment.

Medical history was extracted from medical record or the TAPhOD database. Risk of HBV infection including maternal history of HBV infection, history of blood transfusion and sexual history was assessed by interview.

Laboratory measurements

Hepatitis B serostatus was determined by serologic testing which included hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis core antibody (anti-HBc). HBsAg detection was performed by Microparticle Enzyme Immunoassay (MEIA), or Enzyme-linked immunosorbent assay (ELISA) test or Immunochemiluminescence (CMIA). Anti-HBs, and anti-HBc were measured using the Abbott AxSYM system (Wiesbaden, Germany), ELISA, or CMIA.

HBV-HIV Co-infection was defined as persistent positive HBsAg, resolved natural infection was defined as having both anti-HBc and anti-HBs positive, and seroprotective antibody from immunization was defined as having anti-HBs ≥ 10 mIU/mL with negative antiHBc [11]. Children with HBV-HIV co-infection had a second blood drawn to test for the presence of HBe Ag, anti-HBe, HBV DNA level and lamivudine resistance mutation. HBe Ag and anti-HBe were measured by Abbott AxSYM, Microparticle enzymatic immunoassay (MEIA) at the HIV-NAT laboratory.

HBV DNA was measured by a real-time PCR assay with a limit of detection of 100 copies/mL [12,13]. HBV genotype was determined by comparing with each complete HBV genome sequences. Phylogenetic analysis was constructed by Molecular Evolutionary Genetics Analysis (MEGA) software version 3.1 [13]. HBV Mutation Analysis assessed the presence of rtM204V/I by pinpointing the change in the YMDD motif; HBV nucleotides were translated into amino acid sequences using the translation tool provided by the ExPASy Proteomics Server (available at: <http://www.expasy.ch/tools/dna.html>) [14] at the Center of Excellence in Clinical Virology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University. The whole genome HBV sequences obtained from this study were submitted into the GenBank database with the accession no. JN827414–JN827425. Alanine aminotransferase (ALT) was considered elevated using a cut-off >30 IU/L [15].

Statistical analysis

The prevalence of HBV-HIV co-infection, resolved natural infection, and HBV seroprotection were reported as a proportion with 95% confidence intervals. The Chi square test or Fisher's exact and logistic regression analysis were to make comparisons between groups. All analyses were performed using the Statistical Package for Social Science version 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

From Nov 2010 to Mar 2011, 521 patients were enrolled; 227 (44%) were male; their mean age (SD) was 14.8 (2.1) years. Only 15 adolescents (3%) were born before 1992 when routine HBV immunization was not implemented in Thailand. Their mean current CD4 lymphocyte count (SD) was 685 (324) cells/ μ L and 86% were virologically suppressed. Two hundred and eighty one cases (54%) had either reported or documented HBV vaccination during childhood. Seventy-five of 521 (14%) had received a 3-dose HBV revaccination after immune recovery as a result of antiretroviral treatment. The median time between revaccination and blood draw for this study was 4.3 (IQR 3.7–4.5 years). Risk factors for HBV other than perinatally transmission were previous blood transfusion in 10 cases (2%), and history of engaging in sexual activity in 40 cases (8%). Hepatitis B serostatus stratified by study site is shown in Table 1. Seventeen children were HBV/HIV

co-infected [3.3%; 95% CI: 1.9% to 5.2%]. A comparison of characteristics among those with and without HBV co-infection is shown in Table 2. Among 15 cases born before 1992, one case (6.7%) had positive HBsAg and one (6.7%) had resolved natural infection. Three of those who had hepatitis B revaccination after HAART had protective antibody against hepatitis B

The clinical characteristics of 17 adolescents with chronic HBV infection are summarized in Table 3. Mean (SD) age and CD4 lymphocyte count were 16.3 (2.3) years and 591 (277) cells/ μ L. Eleven of 16 (69%) had HBV DNA $> 10^5$ copies/mL. Only 2 cases had HBV DNA < 100 copies/mL; one was currently treated with lamivudine and tenofovir. HBeAg was presented in 14/16 cases (88%) while anti-HBe was presented in only 1/16 (6%). Anti-HBc could not be detected in 5 cases. There were 6 participants (35%) with elevated ALT > 30 IU/L. Current antiretroviral drugs included lamivudine (88%) and tenofovir (12%). Resistance to lamivudine was detected in 9 of 12 cases tested (75%).

Resolved natural infection was found in 8 cases [1.5%; 95% CI: 0 to 3%]. None of them had documented or recalled a history of clinical hepatitis. Isolated core antibody (Anti-HBc) was detected in 4 cases [0.8%; 95% CI: 0 to 2%]. Ninety-six cases (18%) had protective antibody against HBV with a significantly higher proportion found among adolescents who received HBV revaccination after receiving antiretroviral therapy (93% vs. 6%, $p < 0.01$). The characteristics of participants with and without protective antibody against hepatitis B are shown in Table 4. The group with protective antibody had higher mean age, higher CD4 lymphocyte count, and a higher proportion had been previously immunized against HBV.

Discussion

The prevalence of HBV/HIV co-infection is 3.3% in perinatally HIV-infected Thai adolescents receiving ART. Only 18% of adolescents had protective antibody against hepatitis B virus. Approximately 70% of adolescents with HBV co-infection had high HBV DNA and lamivudine resistance associated mutations.

The prevalence of HBV co-infection in our study was higher than that reported among a non-HIV-infected, healthy Thai population. Data from a countrywide HBsAg seroprevalence survey conducted in 2004 showed a prevalence of 4.4% and 0.82% among those who were born before 1992 and after 1992, respectively [16]. Almost all (97%) of participants in our study were born after national universal hepatitis immunization was implemented in Thailand provides evidence that hepatitis B infection is more prevalent in HIV-positive Thai children.

The HIV-HBV co-infection prevalence in our study is lower than that reported in other Asian and African countries. A Chinese study demonstrated HBV co-infection among 4.9% of children with a median age of 7 years [9]. HBsAg seroprevalence in our study was slightly lower, while the prevalence of HBV carriers in general population was similar at around 10% [7, 8]. A study conducted in HIV-infected Nigerian children aged from 10 months to 17 years, reported the prevalence of HIV/HBV co-infection was 7.7%, while the prevalence of HBs Ag in Nigerian adults ranged from 7.5 to 44.7% [17] while studies in HIV-infected Kenyan children aged 0–12.7 years (2003) and Tanzanian children ages ranged from < 2 to > 15 years (2006) have reported positive HBsAg in 4% and 1.2%, respectively [18, 19].

Five adolescents with HBV-HIV co-infection in our cohort had negative anti-HBc, and this could probably be explained by false negative anti-HBc result, since HBV DNA was detected in 4 out of 5 of these cases. All of them were viral suppressed and in good immune status with current CD4 lymphocyte count ranged from 376–920 cells/ μ L.

We found isolated core antibody in 4 cases (0.8%), none had detected HBV DNA. This meant natural infection has been occurred without antibody response to protective level (negative anti-HBs when the cut-off 10 mIU/mL was used), or antibody response might have happen but subsequently waning with time. All of them were female, at ages ranged between 12.2–15.9 years which were not different from mean age of participants in this cohort. An adult HIV study in Taiwan where HBV infection was hyperendemic reported the prevalence of isolated Anti-HBc is 17.5%, with HBV DNA detectable in 8.3% of those patients. The authors suggested this might be related to old age and low CD4 lymphocyte count of the study participants [20]. A US study observed that individuals co-infected with HIV and hepatitis C virus were more likely to have isolated core antibody (anti-HBc) than HIV infected individuals without hepatitis C infection [21]; they claimed that it was associated with the severity of immune suppression. As the current CD4 lymphocyte count of our 4 cases at the time of the study ranged from 260–1327 cells/ μ l, it might not be the case. However, the number was too few to find out predictors for isolated core antibody.

Low hepatitis B seroprotective antibody rates (18%) in this study might be due to the primary vaccine failure or waning of immunity during the period of immunosuppression prior to antiretroviral initiation. The P1024US study, also reported that 24% of HIV-infected children receiving antiretroviral therapy were hepatitis B seropositive [22]. Revaccination of hepatitis B vaccines may therefore be needed in this population. We have previously reported that 92% of HIV-infected children with immune recovery after ART had HBV seroconversion after revaccination with a 3-dose recombinant HBV vaccine [23]. Furthermore, the protective antibody against HBV is sustainable in 71% of children on stable on antiretroviral treatment with immune recovery, three years after revaccination [24].

In our study, 75% of children had HBV-3TC associated mutations. This is in line with a previous report that 3TC monotherapy is associated with a high risk of developing the M204V resistance mutation, at a rate of approximately 20–25% per year [25,26]. In our study, the median duration of antiretroviral drug therapy was 7 years. The HBV DNA levels in our study were very high: 69% of children had $> 10^5$ copies/mL. 3TC monotherapy in children was less likely to suppress HBV DNA $< 3 \log_{10}$ copies/mL at week 48 compared to those who received tenofovir plus 3TC (46% versus 92%) [27]. Thus, we propose that HIV adolescents with HBV co-infection should receive combination therapy with tenofovir plus 3TC similar to that recommended in the adult population [28].

There are some study limitations to be addressed. First, we did not have a history of maternal HBV status and information on access to hepatitis B immunoglobulin which are the main factors influencing HBV transmission risk. Second, we conducted our study at tertiary care hospitals which may represent a group of participants with different characteristics than those who received HIV care at local hospital. However, we do not anticipate any difference in HBV prevalence rates at local hospitals, since all our cases were asymptomatic.

A strength of this study comes from the systematic screening for hepatitis B co-infection in perinatally HIV-infected adolescents conducted in four sites, which represent adolescents surviving with HIV in different parts of the country. In addition, we confirmed chronic HBV infection by testing for HBV DNA.

In conclusion, the prevalence of HBV co-infection in HIV-infected Thai adolescents is higher than general population in the era of routine HBV immunization. The prevalence of HBV seroprotection is low despite childhood vaccination, and 80% of HIV-infected adolescents on ART remain at risk for HBV infection. Thus, revaccination with HBV vaccine should be encouraged in this population.

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Table 1

Hepatitis B serostatus stratified by study site

Characteristics	Total	Prevalence (95% CI)	Study site			
			Chiangrai Hospital	Srinagarind Hospital	HIVNAT	RIHES-CMU
Number of HIV-infected children	521		176	148	90	103
Male gender (%)	225 (43.2%)		69 (39.2%)	58 (39.2%)	43 (47.8%)	55 (53.4%)
Mean current age, years (SD)	14.8(2.1)		14.5(2.2)	14.5(1.8)	15.3(2.4)	15.2(2.2)
Hepatitis B serostatus						
-Chronic Hepatitis B	17	3.3 (1.9–5.2)	9	6	1	1
-Isolated core antibody	4	0.8 (0.2–2.0)	1	3	0	0
-Resolved natural HBV infection	8	1.5 (0.7–3.0)	4	3	1	0
-Having seroprotection from previous immunization	96	18.4 (15.2–22.0)	3	7	25	61

Data are in number(%) or mean(SD)

Table 2

Characteristics of HIV-infected adolescents with and without HBV co-infection

Characteristics	HBsAg positive n=17	HBsAg negative n=504	p-value
Male gender, no (%)	6 (35)	221 (44)	0.621
Mean (SD) current age, years	16.3(2.3)	14.7(2.1)	0.004
Mean (SD) current CD4 lymphocyte count (cells/ μ l)	559(253)	689(323)	0.115
Number of cases with viral suppression (HIV RNA < 400 copies/mL), no (%)	11(65)	345(69)	1.000
History of hepatitis B immunization, no (%)	5(29)	276(55)	0.048
History of blood transfusion, no (%)	3(18)	37(7)	0.134
Sexually active by self-report, no (%)	1(6)	31(6)	1.000

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Table 3

Details of 17 adolescents with Hepatitis B and HIV co-infection

No	sex	Age	HBV DNA (copies/ml)	anti-HBc	HBsAg	anti-HBc	ALT (IU/L)	Genotype	HBV-related 3TC resistance	Duration on ART (years)	Currently on 3TC	Currently on Tenofovir	CD4count (cell/ μ l)	HIV RNA (copies/ml)
1	M	13.9	1.44x10 ⁸	neg	pos	neg	18	C5	Yes	8.9	Yes	No	376	<40
2	M	17.4	3.10 $\times$ 10 ⁴	pos	pos	neg	16	ND	ND	9.2	Yes	No	405	<40
3	F	12.8	2.39 $\times$ 10 ⁹	pos	pos	neg	25	C5	No	12.2	No	No	963	<50
4	F	17.3	1.19 $\times$ 10 ³	pos	neg	neg	32	ND	ND	11.8	Yes	No	920	<50
5	M	15.7	8.58 $\times$ 10 ⁶	pos	pos	neg	28	C1	Yes	9.6	No	No	903	<50
6	M	16.9	7.53 $\times$ 10 ⁵	pos	pos	neg	14	C1	No	4.3	Yes	Yes	425	<40
7	M	14.8	ND	pos	ND	ND	23	ND	ND	7.0	Yes	No	754	47
8	F	22.7	< 100	neg	pos	neg	38	ND	ND	7.3	Yes	Yes	583	7.48 $\times$ 10 ⁵
9	M	17.5	2.74 $\times$ 10 ⁸	pos	pos	neg	23	C1	Yes	4.5	Yes	No	865	91
10	F	15.1	7.71 $\times$ 10 ³	pos	neg	pos	26	C1	Yes	4.6	Yes	No	499	8.51 $\times$ 10 ⁴
11	F	16.7	6.27 $\times$ 10 ⁶	neg	pos	neg	20	C1	Yes	5.6	Yes	No	414	213
12	F	18.2	1.52 $\times$ 10 ⁸	neg	pos	neg	41	C1	Yes	8.5	Yes	No	545	6.00 $\times$ 10 ⁴
13	F	16.6	3.66 $\times$ 10 ⁷	pos	pos	neg	37	C1	Yes	3.8	Yes	No	160	1.41 $\times$ 10 ³
14	M	14.3	2.96 $\times$ 10 ⁸	pos	pos	neg	43	B2	Yes	5.9	Yes	No	511	1.60 $\times$ 10 ⁵
15	F	15.4	2.37 $\times$ 10 ⁸	pos	pos	neg	94	C1	Yes	15.8	Yes	No	434	20
16	F	17.2	< 100	pos	pos	neg	23	ND	ND	5.6	Yes	No	190	<40
17	F	13.9	3.45 $\times$ 10 ⁸	pos	pos	neg	12	C1	No	1.8	Yes	No	1092	84

* F female, M male, HBV hepatitis B virus, anti-HBc Hepatitis B core antibody, HBsAg hepatitis B e antigen, anti-HBc Hepatitis B e antibody, ALT alanine transferase, 3TC lamivudine; neg negative, pos positive, ND not done

Table 4

Characteristics of HIV-infected adolescents with and without protective antibody against hepatitis B

Characteristics	Anti-HBs positive n=96	Anti-HBs negative n=425	p-value
Male gender, no (%)	48(50)	179(42)	0.172
Mean (SD) current age, years	15.2(2.0)	14.7(2.2)	0.041
Mean (SD) current CD4 lymphocyte count, cells/ μ l	747(279)	669(333)	0.035
Proportion of cases with viral suppression (HIV RNA < 400 copies/mL), no (%)	87/96(91)	269/321(84)	0.067
History of hepatitis B immunization (by history or documented), no (%)	89(93)	192(45)	<0.001
History of hepatitis B revaccination, no (%)	70(73)	5(1)	<0.001