Published in final edited form as:

Pediatr Infect Dis J. 2018 August ; 37(8): 788–793. doi:10.1097/INF.0000000000001901.

Seroprevalence of Hepatitis B among HIV-infected Children and Adolescents Receiving Antiretroviral Therapy in the TREAT Asia Pediatric HIV Observational Database

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Abstract

Background: Hepatitis B (HBV)-HIV coinfection is associated with liver inflammation, which can progress to liver fibrosis/cirrhosis and hepatocellular carcinoma. We determined HBV seroprevalence in children and adolescents participating in the TREAT Asia Pediatric HIV Observational Database.

Methods: A multi-site cross-sectional study was conducted in HIV-infected patients currently aged <25 years receiving antiretroviral treatment (ART) who had HBV surface antigen (HBsAg), and/or HBV surface antibody (anti-HBs), and/or HBV core antibody (anti-HBc) tested during 2012-2013. HBV coinfection was defined as having either a positive HBsAg test, or being anti-HBc positive and anti-HBs negative, reflective of past HBV infection. HBV seroprotection was defined as having a positive anti-HBs test.

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Disclosures: The authors have no conflicts of interest or funding to disclose.

Results: A total of 3,380 patients from six countries (Vietnam, Thailand, Cambodia, Malaysia, Indonesia, India) were included. The current median (interquartile range; IQR) age was 11.2 (7.8-15.1) years. Of the 2,755 (81.5%) patients with HBsAg testing, 130 (4.7%) were positive. Of 1,558 (46%) with anti-HBc testing, 77 (4.9%) were positive. Thirteen of 1,037 patients with all three tests were anti-HBc positive and HBsAg and anti-HBs negative. One child was positive for anti-HBc and negative for anti-HBs, but did not have HBsAg tested. The prevalence of HBV coinfection was 144/2,759 (5.2%) [95% confidence interval 4.4-6.1]. Of 1,093 (32%) patients with anti-HBs testing, 257 (23.5% ; CI 21.0-26.0) had positive tests representing HBV seroprotection.

Conclusions: The estimated prevalence of HBV coinfection in this cohort of Asian HIV-infected children and adolescents on ART was 5.2%. The majority of children and adolescents tested in this cohort (76.5%) did not have protective HBV antibody. The finding supports HBV screening of HIV-infected children and adolescents to guide revaccination, the use of ART with anti-HBV activity, and future monitoring.

Keywords

Hepatitis B; HIV-infected children; antiretroviral treatment; Asia

The effect of chronic hepatitis B (HBV) infection on overall mortality of HIV-infected individuals has been well-documented [1]. Those with HBV-HIV coinfection are more likely to develop active liver disease and more rapidly progress from liver inflammation to fibrosis and cirrhosis. In 2013, World Health Organization (WHO) guidelines advised HBV screening prior to antiretroviral treatment (ART) initiation and recommended using an antiretroviral therapy (ART) regimen that has activity against both HIV and HBV (lamivudine [3TC] or emtricitabine [FTC] and tenofovir disoproxil fumarate [TDF]) in those with coinfection [2].

The prevalence of HBV infection in HIV-infected adults in Asia has been reported to be between 8-10% [3-4], while reports on prevalence of HBV-HIV co-infection among children and adolescents remain scarce. As chronic HBV infection is related to liver cancer, HBV vaccine is one of a limited number of primary cancer-preventing interventions [5]. HBV immunization has been included in childhood vaccination program of most countries (94%) for more than a decade, and the 3-dose HBV immunization coverage in South-East Asia Region was 74% by the end of 2013 [6]. Thus, the prevalence of HBV infection is expected to be lower than in previous generations. Nevertheless, both primary and secondary vaccine failure have been reported in HIV-infected children, especially in those who have been severely immunosuppressed prior to ART. In a Romanian cohort, adolescents living with HIV were found to have higher prevalence of HBV core antibody (anti-HBc) seropositivity when compared to age-matched controls without HIV infection [7]. Revaccination has been increasingly advised in several countries to ensure HBV protection in adolescents entering sexually active years of life, but it is not yet the standard of care across Asia. There has also been a concern that despite HIV-infected youth may lack protective antibody following HBV infection.

In this analysis we determined the prevalence of HBV co-infection, and compared abnormal alanine aminotransaminase (ALT) and HIV treatment outcomes among HIV-infected and

HBV/HIV-coinfected children and adolescents. We also examined the prevalence of protective antibody against HBV, its association with history of vaccination/revaccination and clinical characteristics of children and adolescents living with HIV.

METHODS

Study population

We conducted a cross-sectional study using data from the TREAT Asia Pediatric HIV Observational Database (TAPHOD) of IeDEA Asia-Pacific (International Epidemiology Databases to Evaluate AIDS). Inclusion criteria were 1) HIV-infected children and adolescents receiving ART, 2) current age <25 years, and 3) having HBV surface antigen (HBsAg), HBV surface antibody (anti-HBs), and/or anti-HBc tested during 2012-2013.

Demographic data included age, sex, route of HIV acquisition, WHO staging, CD4+ T-lymphocyte (CD4) values, plasma HIV RNA level (prior to ART and most recent value), and duration on ART were extracted from the database. History of ever receiving HBV vaccination referred to as any HBV vaccine given during infancy period or early childhood; HBV revaccination included HBV vaccine given to those with a known history of prior primary vaccination (usually after immune recovery with ART). Targeted laboratory results were HBV profile (HBsAg, anti-HBs, anti-HBc) and serum alanine aminotransferase (ALT).

Definitions

HBV coinfection was defined as having either a positive HBsAg test, or being anti-HBc positive and anti-HBs negative, which reflect HBV infection. HBV seroprotection was defined as having a positive anti-HBs test (anti-HBs > 10 mIU/mL). The threshold for elevated ALT was set at 30 IU/L, adopted from the British HIV Association guideline 2012, and was used for both sexes as a marker of liver dysfunction suggesting HBV effects on the liver [8].

Statistical analysis

We used descriptive statistics and calculated the point prevalence (95% CI) of HBV coinfection, protective antibody against HBV, and proportion of patients with liver dysfunction. We reported the association between HBV vaccination/revaccination and protective antibody using logistic regression methods. Age, WHO clinical stage, weight- and height-for-age Z-scores (WAZ, HAZ) at the date of anti-HBs, as well CD4 percent at cART initiation and sex were considered as potential confounders. Factors found to be significant at the $P < 0.10$ level in univariate analysis were subsequently tested in multivariate analysis. A two-sided $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using Stata statistical software, version 13.1 (StataCorp LP, College, Station, TX).

RESULTS

Cohort characteristics

We included data from 3,380 patients who received ART at 18 clinical sites in six countries (Vietnam, Thailand, Cambodia, Malaysia, Indonesia, and India); 96% had reported perinatally acquired HIV infection. The current median (interquartile range; IQR) age was 11.2 (7.8-15.1) years, and duration on ART was 5.9 (3.4-8.0) years. History of HBV vaccination either prior to ART or at any time during follow-up was noted in the available medical records of 1,565 patients (39%).

Prevalence of HBV-HIV coinfection

Of the 2,755 (81.5%) patients with HBsAg testing, 130 (4.7%) were positive. Of 1,558 (46%) with anti-HBc testing, 77 (4.9%) were positive. Thirteen of 1,037 (1.3%) patients with all three tests were anti-HBc positive and HBsAg and anti-HBs negative. One child was positive for anti-HBc and negative for anti-HBs but was not tested for HBsAg. The prevalence of HBV coinfection was 144/2,759 (5.2%) [95% confidence interval (CI) 4.4-6.1]. (Figure 1) For the group with HBV-HIV coinfection, their median (IQR) current age was 11.6 (8.1-14.7) years; 65 (50%) were male; their median (IQR) current CD4 count 802 (558-1172) cells/mm³; and 84% (49/58 with available HIV RNA testing results) had HIV RNA <400 copies/mL. (Table 1) There was no statistically significant difference between the evaluated characteristics of those with HIV infection alone and HBV-HIV coinfection. Among the 77 patients with positive anti-HBc tests, 76 were tested for HBsAg and 30 (39%) were HBsAg positive (another one had missing data). Thirty-six of 76 (47%) were tested for anti-HBs, and six (17%) were anti-HBs positive.

Treatment outcome and response to ART

There was no significant difference in immunologic or virologic outcome after ART initiation among HIV-infected and HBV-HIV coinfecting patients (Table 1). Of 95/144 (66%) with serum ALT available prior to ART, 34 (36%) had grade 1-2 ALT levels. At the time of the study, 31/34 (91%) had normalized serum ALT, while one patient had improved from grade 2 to grade 1 ALT levels, and another two with grade 1 and 2 ALT remained at the same grade. Six patients with a normal ALT (grade 0) at ART initiation increased to grade 1 (N=4) and grade 2 (N=2) at the time of the study. The proportion of patients with abnormal ALT was not significantly different from those with HIV infection alone.

Prevalence of HBV seroprotective antibody (Figure 2)

Of 1,094 (32.4%) patients with anti-HBs testing, the prevalence of HBV seroprotection was 23.5% (95%CI 21.0-26.0). There were 651 patients with a history of primary HBV vaccination; of these, 267 were revaccinated after ART: 97/172 (56.4%) with 3-dose and 23/95 (24.2%) with single- or 2-dose regimen were subsequently positive for anti-HBs. Among those who were not revaccinated, the prevalence of seroprotection (anti-HBs positive) were 4/46 (9%) for patients who had received 1-2 doses, and 56/338 (17%) for those with a completed 3-dose primary vaccination. A higher proportion of children with history of WHO stage 3-4 received HBV revaccination (45% vs. 36%, p=0.02).

In the multivariate analysis conducted among 651 children with available complete or partial vaccination histories, completed childhood vaccination (odds ratio [OR] 3.3, 95% CI 1.6-6.8), revaccination (OR 5.1, 95%CI 3.3-7.7), older age (age >5 years [OR 2.52, 95%CI 1.42-4.48], age 13 years [OR 13.4, 95%CI 4.25-42.47]), current CD4 >25% (OR 5.01, 95%CI 1.74-14.46), and receiving ART for 3 years when tested for anti-HBs (OR 6.28, 95%CI 3.10-12.72) were found to be associated with having HBV seroprotective antibody (Table 2).

DISCUSSION

The estimated prevalence of HBV co-infection in HIV-infected children and adolescents in our cohort was 5.2%, which is similar to previous reports in this region. A Cambodian study of 974 HIV-infected children documented HBV infection in 45 (4.7%) [9]. The prevalence in a study of Chinese HIV-infected children was 4.9% (53 of 1082) [10]. A Thai study among 521 HIV-infected adolescents (mean age of 14.8 ± 2 years) reported the prevalence of HBV coinfection at 3.3% [11]. While the HBV infection prevalence in HIV-infected adults reported from a multi-country study that included two Asian countries (India and Thailand) was 5.9% [12], a more recently published article from a multi-center cohort of HIV-infected patients in the Asia-Pacific region reported that 10.4% (591 of 5656 patients tested) were HBsAg positive [13]. However, it is worth noting that all of these results were limited by varying proportions of patients who were tested. In addition, a lower HBV prevalence in HIV-infected children could reflect the effect of HBV vaccination in this new generation, combined with a reduced risk of sexually acquired infections due to younger age.

The beneficial generational effect of vaccination may be a factor in the relatively lower rates of HBV coinfection compared to older African studies. Reported prevalence's of HBV-HIV coinfection in children have been somewhat higher in Nigeria (7.8%) [14], Zambia (10.4%) [15], and the Ivory Coast (12.1%) [16]. Notably, the prevalence rates of HBV co-infection in children were not higher than the population averages in Asia and Africa (8-20%) [10], despite the presence of HIV coinfection.

In HIV-infected adolescents newly diagnosed patients would benefit from HBV screening to ensure that those with HBV infection include tenofovir with emtricitabine or lamivudine in their first ART regimen. While young children with HBV coinfection may remain in the immune tolerant phase with hepatitis B e antigen positivity, high levels of HBV DNA and normal hepatic function, regular monitoring during the course of ART would guide the need for treatment regimen modification. For those with chronic HBV, apart from ALT monitoring as a part of HIV care, in settings where HBV DNA testing is available and accessible, full assessment to determine staging of HBV infection would be beneficial.

In this cohort, the HIV treatment outcomes as measured by the proportion of cases with normalization of CD4 count (>500 cells/mm³) and HIV virologic suppression (<400 copies/mL) were not different between the two groups. The prevalence of abnormal ALT among HBV-HIV coinfecting patients in our cohort was similar to those with HIV mono-

infection. However, we did not test for HBeAg status of those with HBV-HIV coinfection and increased ALT. Thus, we could not categorize whether the patients were immunoactive.

Even though universal infant HBV vaccination is recommended in most national programs worldwide, according to the data from CDC in 2013, the global HBV vaccination coverage was 81%. In South-east Asia the HBV vaccination coverage was only 26% and 74% for birth dose and 3-dose course, respectively [17]. In this study we found that two-thirds of patients tested had no protective antibody against HBV, regardless of childhood vaccination history. This was comparable to a Cambodian study among 974 HIV-infected children. Of 381 of these children with a history of primary HBV vaccination (either from the national program at birth or from private clinic after birth), 293 (77%) had no protective antibody against HBV. After ART initiation, 3-dose HBV revaccination was given at the median age of 8.6 years, the seroresponse rate was 62%. [9]. Another study in HIV-infected Thai children who completed a 3-dose HBV vaccination series showed that 90% developed protective anti-HBs [18]. In the WHO position papers, HBV vaccination is recommended for HIV-infected individuals as early as possible after HIV diagnosis, and also remarked that immune response after vaccination might reduce in immunocompromised population [19]. Currently HBV revaccination programs for HIV-infected children and adolescents have not yet been consistently implemented in many countries in the Asia-Pacific region where prevalence of HBV infection is high. Our study results support that HBV revaccination should be offered to those who initiated on ART when their CD4 counts were low. An important barrier in Thailand and many countries is that patients have to pay for vaccines outside of national programs for routine infant and childhood immunization. Apart from vaccination, we found other factors which were associated with having HBV seroprotective antibody, including older age, immune recovery (by CD4 count), and duration on ART 3 years.

From our data, 5.2% of patients had evidence of HBV infection either determined from positive anti-HBc or HbsAg tests. Some of them may not have received primary HBV vaccination during their childhood (e.g., if they resided in a remote area or were refused due to early concerns over perinatal HIV infection). Another possibility was waning immunity after primary vaccination in the context of severe immunodeficiency, which could have exposed these children to a higher risk of post-natal infection. We found that 10 of 13 patients with isolated anti-HBc had documented history of HBV vaccination, suggesting breakthrough infection. Revaccination after immune recovery is recommended to ensure protective antibody in those with waning immunity, and to protect those who may have missed their primary vaccination series. For the isolated HBV core antibody, which was observed in 1.3% of HIV-infected children and adolescents in this study, usually there were 3 different explanations: resolved infection (most common), low-level chronic infection, or resolving acute infection. In a Taiwan cohort of HIV-uninfected students with history of complete HBV vaccination during infancy, the prevalence of isolated core antibody was 1.2% [20]. In that study, they found no evidence of occult HBV infection and they also reported that seroresponse to a single booster dose of HBV vaccine in this group was not different from a control group without core antibody. The clinical significance of isolated HBV core antibody and future transmission risk remain unclear.

Major limitations of this cross-sectional study include that not all patients had a full panel of HBV biomarkers, and vaccination histories were incomplete. This prevented us from conducting a more thorough assessment of seroprotection. As much as 31% of patients had an unknown history of vaccination. However, the prevalence of seroprotection in this group was 23%, which was not substantially different from those who reported ever having been vaccinated prior to ART. Confirmatory testing for chronic disease by HBV DNA, not readily available in routine HIV clinical care settings in most Asian countries, was not performed. In addition, as this is an observational cohort, the completeness of routinely collected data varied from site to site. As these sites were generally tertiary referral centers, the results may not be generalizable across differing clinical settings or be representative of national outcomes.

In summary, we reported that the prevalence of HBV coinfection in this cohort of Asian HIV-infected children and adolescents on ART was 5.2%. Many patients who were tested were found to have no HBV protective antibody. At the time of ART initiation, HBV screening of HIV-infected children and adolescents can guide use of ART with anti-HBV activity, and HBV retesting in older HIV-infected children and adolescents after immune recovery would guide revaccination practices in order to protect them from acquiring HBV infection in the future. Further study to track the long-term hepatic outcomes and natural history of perinatally HBV-HIV coinfecting persons is warranted.

Acknowledgement

The TREAT Asia Pediatric HIV Network:

PS Ly*, and **V Khol**, National Centre for HIV/AIDS, Dermatology and STDs, Phnom Penh, Cambodia;

J Tucker, New Hope for Cambodian Children, Phnom Penh, Cambodia;

N Kumarasamy*, **S Saghayam**, and **E Chandrasekaran**, YRG CARE Medical Centre, CART CRS, Chennai, India;

DK Wati*, **LPP Atmikasari**, and **IY Malino**, Sanglah Hospital, Udayana University, Bali, Indonesia;

N Kurniati*, and **D Muktiarti**, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia;

SM Fong*[†], **M Lim**, and **F Daut**, Hospital Likas, Kota Kinabalu, Malaysia;

NK Nik Yusoff*, and **P Mohamad**, Hospital Raja Perempuan Zainab II, Kelantan, Malaysia;

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ON Le, Worldwide Orphans Foundation, Ho Chi Minh City, Vietnam;

AH Sohn*, **JL Ross**, and **C Sethaputra**, TREAT Asia/amfAR -- The Foundation for AIDS Research, Bangkok, Thailand;

DA Cooper, **MG Law***, and **A Kariminia**, The Kirby Institute, UNSW Australia, Sydney, Australia;

Funding Sources

The TREAT Asia Pediatric HIV Observational Database is an initiative of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Cancer Institute as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA; U01AI069907), and the LIFE+, Austria. The Kirby Institute is funded by the Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, UNSW Australia. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the governments or institutions mentioned above.

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Figure 1.
Number of study participants and HBV serologic testing performed

Figure 2. Anti-HBs serostatus of study participants grouped by Hepatitis B vaccination history
Abbreviations: anti-HBs hepatitis B surface antibody; ART antiretroviral treatment; HBV hepatitis B virus

Table 1

Hepatitis B serologic tests performed in study participants (n=3,380)

HBsAg testing	Anti-HBs testing	Anti-HBc testing	Number of patients
✓	✓	✓	1037
✓	✓		53
✓		✓	490
	✓	✓	4
✓			1175
	✓		0
		✓	27
2755	1094	1558	

Table 2

Demographic characteristics of 2,759 children and adolescents with and without HBV coinfection

Characteristics	HIV monoinfection	HBV-HIV coinfection	p-value
Total number of patients	2615	144	
Male sex	1342 (51.3)	69 (47.9)	0.44
Age (years) at cART initiation,	5.1 (2.5-8.0)	4.7 (2.3-9.1)	0.69
Prior to cART			
CD4 percentage	11 (4-18)	12 (5-19)	0.48
< 15	1361 (52.0)	72 (50.0)	0.32
15- < 25	526 (20.1)	22 (15.3)	
25	212 (8.1)	14 (9.7)	
Unknown	516 (19.7)	36 (25.0)	
CD4 lymphocyte count (cells/mm ³)	278 (71-648)	268 (90-634)	0.99
< 200	887 (33.9)	44 (30.6)	0.24
200-349	335 (12.8)	26 (18.1)	
350-499	211 (8.1)	9 (6.3)	
500	695 (26.6)	33 (22.9)	
Unknown	487 (18.6)	32 (22.2)	
HIV RNA level >10,000 copies/mL	627 (24.0)	33 (22.9)	0.99
Unknown	1915 (73.2)	109 (75.7)	
WHO clinical staging at cART initiation			0.98
Stage I/II	963 (36.8)	57 (39.6)	
Stage III	802 (30.7)	43 (29.9)	
Stage IV	361 (13.8)	19 (13.2)	
No event documented	489 (18.7)	25 (17.4)	
First cART regimens *			<0.01
NVP-based	1629 (62.3)	75 (52.1)	
EFV-based	777 (29.7)	62 (43.1)	
Current cART regimens			0.58
Include 3TC but no TDF	2146 (82.1)	116 (80.6)	
Include both TDF and 3TC	357 (13.7)	22 (15.3)	
Current age (years)	11.1 (7.8-14.8)	12.0 (8.2-15.3)	0.28
< 5	233 (8.9)	15 (10.4)	0.33
5- < 13	1425 (54.5)	70 (48.6)	
13- < 20	890 (34.0)	55 (38.2)	
20-25	67 (2.6)	4 (2.8)	
Current CD4 lymphocyte count (cells/mm ³)	795 (549-1090)	783 (535-1165)	0.93
< 200	106 (4.1)	8 (5.7)	0.67
200-349	137 (5.2)	6 (4.2)	
350-499	264 (10.1)	17 (11.8)	
500	20.16 (77.1)	106 (73.6)	
Unknown	92 (3.5)	7 (4.9)	

Characteristics	HIV mono-infection	HBV-HIV coinfection	p-value
Current HIV RNA level (copies/mL)			
< 400	1246 (47.7)	59 (50.0)	0.32
400-4999	69 (2.6)	5 (3.5)	
5000-9999	25 (1.0)	0	
10000	120 (4.6)	6 (4.2)	
Unknown	1115 (44.2)	74 (51.4)	

HBsAg hepatitis B surface antigen; ART antiretroviral treatment; IQR interquartile range; WHO World health organization

NVP nevirapine; EFV efavirenz; 3TC lamivudine; TDF tenofovir disoproxil fumarate

Data in median (IQR) or number (%) or proportion (%) as appropriate

* Used in combination with nucleoside reverse transcriptase inhibitor backbone: lamivudine and either stavudine or zidovudine or tenofovir

Table 3

Factors associated with having HBV seroprotective antibody in patients with available vaccination and/or revaccination history (n=651)

	Total patients	Total patients	Anti-HBs positive	Univariate			Multivariate		
				OR	95%CI	p-value	OR	95%CI	p-value
Primary vaccination									
Complete	567	168	168	2.5	(1.3, 4.8)	0.004	3.3	(1.6, 6.7)	0.001
Incomplete	84	12	12						
Revaccination									
Yes	267	120	120	4.4	(3.1–6.4)	<0.001	5.0	(3.2–7.7)	<0.001
No	384	60	60						
Age at ART (years)									
< 5	319	63	63						
5–12	306	106	106	2.2	(1.5–3.1)	<0.001	2.9	(1.9–4.4)	<0.001
13	26	11	11	3.0	(1.3–6.8)	<0.001	15.3	(5.2–45.2)	<0.001
WHO stage at ART									
1 or 2	311	97	97	1.4	(1.0–2.0)	0.054	1.7	1.1–2.6	0.011
3 or 4	340	83	83						
CD4 percentage at anti-HBs test									
< 15	46	5	5						
15–24	132	29	29	2.3	(0.8–6.4)	0.106	2.0	(0.7–6.2)	0.214
25	329	124	124	5.0	(1.9–12.9)	0.001	5.0	(1.7–14.4)	0.003
Missing	144	22	22	1.5	(0.5–4.2)	0.458	1.3	(0.4–4.2)	0.615
ART duration at anti-HBs test (years)									
< 3	164	16	16						
3	487	164	164	4.7	(2.7–8.1)	<0.0001	6.3	(3.1–12.7)	<0.001

Anti-HBs hepatitis B surface antigen; OR Odds ratio; CI confidence interval; ART antiretroviral treatment; WHO World health organization