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Risk of Liver Fibrosis in Hepatitis B Virus and HIV Coinfected Youths Receiving Tenofovir-Containing Antiretroviral Regimen

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Abstract

Background: Hepatitis B virus (HBV) and HIV coinfection is associated with risk of progression to chronic liver disease. We assessed liver stiffness in HBV-HIV coinfected youths. **Methods:** A cross-sectional study in HBV-HIV coinfected youths aged 18 to 25 years who received a tenofovir (TDF)-containing antiretroviral therapy regimen for >96 weeks. Measurements included HBV DNA level, HBV serology profiles, and transient elastography (TE). The cutoff for TE results included ≥5.9 kPa for F2-moderate fibrosis, ≥7.4 kPa for F3-severe fibrosis, and ≥9.6 kPa for F4-cirrhosis. **Results:** From March to December 2016, 15 HBV-HIV coinfected youths with a median duration on TDF-containing regimens of 3.3 years were enrolled. Five (33%) youths had significant liver fibrosis, 3 with F2-moderate, 1 with F3-advanced fibrosis, and 1 with F4-cirrhosis. Other 5 without liver fibrosis had hepatitis B surface e antigen (HBsAg) and hepatitis B surface e antigen (HBeAg) loss. Higher mean alanine transaminase (ALT) was observed among the group with F2-F4 when compared to those with F0. **Conclusion:** Liver fibrosis was evidenced in HBV-HIV coinfected youths in Thailand. Transient elastography might be considered for those who do not achieve HBsAg loss or have persistent ALT elevation while on treatment.

Keywords

liver fibrosis, HBV-HIV coinfection, youths, antiretroviral treatment

What Do We Already Know about This Topic?

People living with hepatitis B virus/HIV (HIV-HBV) coinfection are at greater risk of progression of liver inflammation; the ultimate goal of treatment is to decrease risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma.

How Does Your Research Contribute to the Field?

We assessed liver health in youths living with HBV/HIV coinfection by assessing the prevalence of liver fibrosis, determining proportion of youths with HBV virologic suppression and rate of hepatitis B surface antigen [HBsAg] loss after 96 weeks of tenofovir-containing antiretroviral treatment.

What Are Your Research's Implications toward Theory, Practice, or Policy?

To optimize liver outcomes, youths with HBV/HIV coinfection who do not achieve HBsAg loss, have persistent alanine transaminase (ALT) elevation, or abnormal liver biomarkers should be evaluated for presence of liver inflammation.

Introduction

Hepatitis B virus (HBV) coinfection in people living with HIV is associated with a greater risk of progression of liver inflammation toward liver fibrosis, cirrhosis, and liver-related mortality.[1] Currently, the World Health Organization 2016 treatment guideline recommends early antiretroviral treatment (ART) initiation with regimens that can control both viruses,

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that is, tenofovir (TDF) and either lamivudine or emtricitabine for HIV-infected adults and adolescents with chronic active HBV infection together with efavirenz which is associated with low risk of hepatotoxicity.[2] Data on HIV-infected adults receiving treatment with TDF-including ART regimens have shown its effect on liver fibrosis; regression, stabilization, and progression were possible.[3,4]

The prevalence of HBV coinfection in perinatally HIV-infected children in Asia is around 5%.[5–7] For perinatally HIV-infected children with HBV coinfection growing up into adolescence, it is known that immune-tolerant HBV infection would turn into immune-active phase.[8] By adding TDF in antiretroviral regimen of HBV/HIV coinfected adolescents with 3TC-experienced, our previous study[9] has demonstrated 61% HBV viral suppression at week 48. However, the ultimate goal of treatment of chronic HBV infection is to decrease the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma. We assessed the prevalence of liver fibrosis among HBV-HIV coinfected youths who received TDF-containing ART regimens. Hepatitis B virus suppression and rate of HBsAg loss after 96 weeks of treatment were also determined.

Materials and Methods

Study Population

A cross-sectional descriptive study was conducted at Chiang Mai University Hospital, Thailand in 2016. Inclusion criteria were (1) having chronic HBV-HIV infection, (2) aged between 18 and 25 years, and (3) received a TDF-containing ART regimen for >96 weeks. The study participants were recruited from both pediatric and adult HIV clinics in the hospital and neighboring hospitals where potential participants attended for HIV care. Those clinics provided ART to people living with HIV within the catchment area, according to their health-care coverage programs. All eligible patients were approached and invited to join the study by study staff during regular visits.

Data Collection and Measurement

Demographic information and clinical data were reviewed from medical record of each participant. Diagnosis of liver stiffness and fibrosis was assessed by transient elastography (TE) using a Fibroscan (transient elastometer; Echo Sens, Paris, France). The measurement was performed by gastroenterologist following standard procedure.[10] Blood for liver function test (aspartate [AST] and alanine aminotransferase [ALT], respectively), HBV profile (HBsAg, HBeAg, anti-HBe, and anti-HBs), and HBV DNA level was collected. Liver function test (AST, ALT) was performed at study site; liver fibrosis markers; AST-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) were calculated. HBsAg, HBe Ag, and anti-HBe were measured by Abbott Architect, microparticle enzymatic immunoassay; HBV DNA was measured by Abbott real-time PCR assay limit of detection of 10 to 10^9 IU/mL). The assay was performed at HIV-NAT, Thai Red Cross AIDS Research center laboratory.

The primary study outcome was prevalence of liver fibrosis, defined as having liver stiffness measured by TE $\geq$5.9 kPa. The cutoff for TE results included 5.9 to 7.3 kPa for F2-moderate fibrosis, 7.4 to 9.6 kPa for F3-severe fibrosis, and $\geq$9.6 kPa for F4-cirrhosis.[4] The APRI was calculated by ([AST/upper limit of normal]/platelet count [10^9/l]) $\times$ 100; a value of >1.5 suggests liver fibrosis.[11] The FIB-4 index was calculated by age $\times$ AST level/platelet count $\times$ $\sqrt{}$ALT; a value of $\leq$1.3 was reported to have a 90% negative predictive value for cirrhosis.[12] The cutoff for normal ALT was <30 IU/mL. Increase in ALT suggests liver inflammation. Other study outcomes included the rate of HBV virologic suppression, defined as HBV DNA <60 IU/mL (equivalent to 300 copies/mL) and incidence of HBsAg and HBeAg loss after receiving TDF-containing ART.[13]

Statistical Analysis

Using the SPSS Statistics for Windows, version 17.0. (SPSS Inc, 2008), descriptive statistical analysis was performed. Continuous variables were presented as mean (standard deviation) or median (range or interquartile range [IQR]), as appropriate. Categorical variables were presented in number (percentage). Student *t* test was used in comparison of ALT between groups. A P value of <.05 for 2-sided tests was considered to be statistically significant.

Results

From March to December 2016, 15 HBV-HIV-infected youths with median age of 23.0 (IQR: 19.8-24.4) years were enrolled. Eight (53%) of them were male; 10 (67%) had perinatal-, and 5 (33%) had behavioral-acquired HIV infection.

The median duration on TDF-containing ART regimens was 3.3 years (IQR: 2.6-3.8 years). The median CD4 lymphocyte count was 678 cells/mm^3 (IQR: 574-777). Twelve of 15 (80%) youths were HIV virologic-suppressed (HIV RNA < 40 copies/mL) at the time of study. There were 5/15 (32%) youths with significant liver fibrosis; 3 (20%) had F2-moderate fibrosis, 1 (6%) had F3-advanced fibrosis, 1 (6%) had F4-cirrhosis. A higher proportion of perinatally HIV-infected youths (4/10) had liver fibrosis when compared to those with behavioral acquired HIV infection (1/5). The clinical information of these 5 patients is shown in Table 1. The one with F4-cirrhosis was the single patient who had abnormal APRI, and FIB-4; he was a 25-year-old male with perinatal HIV infection and a history of dyslipidemia, frequent alcohol use, and hepatitis C negative. The median ALT was higher among the group with liver fibrosis (31 U/L [IQR: 28-62]); however, it was not statistically significant when compared to the group without (15 U/L [IQR: 11-32]), P = .06. Fourteen (93%) of patients in this study, including all 5 patients with presence of liver fibrosis, had HBV DNA <200 IU/mL. HBsAg loss was observed in 5 (33%) patients; none of them had liver fibrosis.

Table 1. Characteristics of HBV-HIV Coinfected Youths in the Study.

No.	Sex	Age (Years)	Body Mass Index (kg/m^2)	Duration of Known HBV[a] (Years)	Duration on Tenofovir-Including ART (Weeks)	Current CD4 (Cells/mm^3)	Current HIV RNA (Copies/mL)	Liver Stiffness (kPa)[b]	METAVIR Score	ALT (IU/L)	HBV DNA (IU/mL)	HBeAg Status
1	M	26	17.9	5.4	186	771	<20	20.6	F4	84	<10	Positive
2	M	16	27.0	3.3	124	337	<20	8.9	F3	39	13	Positive
3	F	21	20.3	11.2	145	719	<40	6.1	F2	28	102	Positive
4	F	23	18.3	3.5	267	581	<20	6.0	F2	27	15	Positive
5	F	26	17.7	12.0	168	899	<20	5.9	F2	31	22	Negative
6	M	20	16.5	5.1	205	682	<20	4.8	F0	28	49	Positive
7	F	21	19.9	3.8	107	771	<20	5.5	F0	10	38	Positive
8	M	15	17.7	2.9	127	719	<40	5.0	F0	19	141 525	Positive
9	M	25	17.3	4.6	172	592	<20	5.3	F0	52	31	Positive
10	F	24	16.6	4.7	219	581	<20	3.4	F0	42	38	Positive
11	F	24	14.8	3.6	174	1325	213	3.2	F0	15	10	Negative
12	F	19	16.8	12.0	161	899	<20	3.7	F0	14	10	Negative
13	M	19	18.9	3.2	196	1153	<20	5.7	F0	11	10	Negative
14	M	26	21.5	4.7	244	337	<20	4.5	F0	15	10	Negative
15	M	23	21.4	2.7	101	522	92	4.9	F0	11	10	Negative

Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus.
[a]Duration from the first documented hepatitis B serology testing as the exact onset of infection was not known.
[b]Liver stiffness was measured by transient elastography.

Discussion

Liver fibrosis by TE was detected in one-third of asymptomatic HBV-HIV coinfected youths who were HBV virologically suppressed on TDF-including ART regimens. Slight ALT elevation was also observed. Currently, there is no clear guideline how to manage, intervene, or monitor for liver disease progression, especially in young population. However, the proportion of perinatally HIV-infected youths with liver fibrosis was higher than expected. Although the exact period of HBV acquisition was not known, with the hypothesis that HIV and HBV were acquired at the same time, the lower prevalence with liver fibrosis among youths with behavioral-acquired HIV infection might be explained by a shorter duration of infections.

Available evidence suggests that immune-tolerant HBV infection would turn into immune-active phase in a decade or more after the acquisition of HBV infection.[8] Hence, a population infected at birth with HBV would most likely enter immune active phase of HBV infection by the time they reach adolescent years. Moreover, chronic HIV infection is associated with occurrence of fatty liver, as reported in a previous Thai study in which 15% of adolescents living with HIV, median age 17.2 years, and have fatty liver detected by ultrasonography.[14] Alcohol consumption might explain worsening of liver pathology in the single male patient with F4-cirrhosis, but not in others without history of alcohol use. No ongoing concurrent medication was reported by any study participant. Severity of liver change might relate to the different genotype of HBV like in the case of HCV infection[15] and need further study to explore.

The Ghanian study reported median TE values of 5.7 kPa in HBV-HIV-infected adults after a median of 45 months on lamivudine treatment and further decreases by a mean of −0.2 kPa in subsequent 12 months after adding TDF.[16] In our study, the median TE values of HBV-HIV-infected youths was 5.3 kPa at the mean duration of TDF 3.3 years; we did not have baseline TE prior to ART or before TDF-based regimen initiation. It is expected that combined TDF and lamivudine treatment, which led to HBV viremic control in most patients, would help in protecting against or at least slow rate of liver fibrosis development. However, a prospective French Cohort study reported both progression (in 15%) and regression (in 17%) of liver fibrosis were possible during treatment with TDF.[3] Associated factors included male sex, age> 40 years, low CD4 lymphocyte count, coming from HBV endemic country, being anemic, or had high fasting glycemia at the time of TDF initiation. Extrapolated from those adult studies, liver stiffness should not progress if both HIV and HBV viral replication was controlled with effective treatment. We found 93% of HBV-HIV-infected youths had undetectable HBV DNA (<200 IU/mL) at a median duration of 3.3 years on TDF-including ART regimens. This was similar to what has been reported in review articles of 550 HBV-HIV coinfected patients treated with TDF; 85.6% had HBV suppression at 3 years.[17] Another US study reported 65% undetectable HBV DNA among HBV-HIV coinfected adults treated with TDF at the median follow-up time of 5 years. However, having HBV virologic suppression per se might not be sufficient to ensure favorable liver outcome.

The mean ALT of the group with liver fibrosis was higher when compared to those without, although not statistically significant. Association between ALT, liver fibrosis, and HBV coinfection in HIV-infected patients were previously mentioned. From the Zambian study, HBV-HIV coinfected adults had significantly higher mean ALT and increase liver stiffness when compared to those with HIV monoinfection.[18] HBV-HIV

coinfected patients with persistent ALT elevation should be further investigated.

A French study documented cumulative incidence rate of HBsAg loss as 4% in HBV-HIV coinfected adults at the median folow-up time of 2.5 years.[19] In this study, HBsAg loss was observed in 5/15 (33%) HBV-HIV coinfected youths; all had no evidence of liver fibrosis. Early effective treatment for treating HBV-HIV coinfection is therefore encouraging, especially in young population.

Our study is firstly limited for its small sample size. As HBV vaccine has been included in the national immunization program since birth with high coverage rate, we found that the prevalence of HBV-HIV coinfection in youths was low. The study results might not be much generalizable; however, it could inform health care workers who are taking care of youths living with HIV to be aware of liver health. Secondly, the study results might not reflect outcomes. Hepatitis B virus-HIV-infected patients who did not appear due to different reasons such as relocation to other places or poor adherence and lost to follow-up. These population of patients may have differences in clinical characteristics and liver pathology from those who adhered to ART and enrolled into the study. Thirdly, we did not have baseline information to compare whether the liver pathology existed right before ART or developed later during the course of treatment.

In resource-limitted setting, although HBV DNA is not routinely monitored, the majority of patients are expected to become HBV virologic suppression on TDF-including treatment regimens. Alternative approach is to monitor HBsAg and ALT in patients with HBV-HIV coinfection, as persistant elevation increases the likelihood of liver disease progression and require further investigation. Elastography techniques should be considered for those who do not achieve HBsAg loss, have persistent ALT elevation, or abnormal liver biomarkers. Consultation with a hepatologist is warranted to optimize liver outcomes by intervening or offering treatment as available.

Authors' Note

The study was approved by the institutional review board at Research Institute for Health Sciences, Chiang Mai University (FWA 00005355), certificate approval number 36/2016. Written informed consent was obtained from each participant prior to enrollment.

Declaration of Conflicting Interests

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