

Screening of Hepatitis B Virus Infection among HIV-Infected Patients Receiving Antiretroviral Therapy

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ABSTRACT

A cross-sectional study was conducted among HIV-infected patients in a university hospital to assess the prevalence of hepatitis B virus (HBV) infection and the effect of antiretroviral therapy (ART) on the results of screening for HBV infection. There were 403 patients with a mean age of 42.3 years and 60.3 percent were male. Median (IQR) CD4 cell count was 395 (277-555) cells/mm³. HBV co-infection was observed in 33 (8.2%) patients. Prevalence of HBV co-infection was 6.1 percent in patients receiving ART at screening and 11.4 percent in patients without ART at screening. In multivariate analysis, the previous AST level prior to the initiation of ART [odd ratio (OR) 1.020; 95 percent confidence interval (CI), 1.007-1.034; p = 0.003] and undetectable HIV RNA at screening [OR 0.243; 95% CI, 0.068-0.870; p=0.030] were significantly associated with the results of screening for HBV co-infection. Liver function test results at screening were not associated with HBV co-infection. Screening for HBV co-infection in HIV-infected patients should not be omitted and should be performed prior to the initiation of ART. (*J Infect Dis Antimicrob Agents* 2010;27:69-75.)

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INTRODUCTION

Hepatitis B virus (HBV) and HIV-1 share the same routes of transmission. Both are principally acquired by sexual transmission. In the United States

and Western Europe, chronic HBV infection is found in 7 percent to 10 percent of HIV-1 infected patients.¹⁻³ Meanwhile the prevalence of HBV/HIV-1 co-infection is higher in Asia Pacific.^{4,5} One study

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showed no impact of HBV infection status on the clinical progression of HIV-1 disease,⁶ whereas some other studies found that the HBV/HIV-1 co-infection was associated with greater mortality than HIV-1 infection alone.^{7,8} A good response to HBV treatment correlates with a successful virological response to HIV-1 treatment with antiretroviral therapy (ART), usually including lamivudine (3TC).⁹ Patients with HIV-1 infection have significant reductions in HBV DNA clearance and HBeAg seroconversion.¹⁰ Knowing the status of HBV infection among HIV-1 infected patients is therefore important for planning of treatment and prevention. Although the screening for HBV co-infection prior to the initiation of ART is generally recommended in Thailand,¹¹ lack of screening for HBV infection is still a problem in resource-limited settings.¹² The purpose of this study was to assess the prevalence of HBV/HIV-1 co-infection and the effect of ART on the results of HBV co-infection screening.

MATERIALS AND METHODS

This is a cross-sectional study in HIV-1 infected patients who visited the infectious disease clinic in a medical school hospital during the 1st and 30th of September 2008. Inclusion criteria was HIV-1 infected patients at an age greater than 15 years old. The patients who did not consent or denied the blood test for hepatitis B surface antigen (HBsAg) were excluded. Baseline data including age, gender, nationality, occupation, date of first diagnosis of HIV-1 infection, risk factors for HIV-1 transmission, date of ART initiation, ART regimen (NNRTI- or PI-based), 3TC experience and duration, liver function test (LFT) prior to ART initiation, nadir CD4 cell count, CD4 cell count, HIV-1 RNA level, LFT, completed blood count (CBC), blood urea nitrogen (BUN) and serum creatinine was collected. HBV infection status was reviewed at the study time. Patients were tested for HBsAg on the study day.

HBsAg was detected using Architect i2000 SR, ELISA Abbott laboratories, IL.

Statistical analysis was performed using SPSS program version 13.0 for Windows (SPSS Inc, Chicago, IL). Study patients were categorized into two groups on the basis of HBsAg screening results. Mean (\pm SD), median (interquartile range, IQR) and frequencies (percentage) were used to show the patients' characteristic in each group. Chi-square or Fisher's exact test was used to compare categorical variables where appropriate. Student's *t*-test and Mann-Whitney *U* test were used to compare the mean and median values of continuous variables. Binary logistic regression analysis was conducted for multivariate analysis to determine the factors associated with HBV co-infection. Factors with *p*-value of less than 0.1 from univariate analysis were included in the multivariate analysis model. A *p*-value of less than 0.05 was considered to be statistically significant. The study was approved by the institutional reviewed board.

RESULTS

A total of 416 patients were eligible for enrollment into the study. Thirteen patients were excluded due to inability to obtain the blood test for HBsAg. Therefore, 403 patients were included into the study for further analysis. The mean (SD) age of the patients was 42.3 (9.8) years and 60.3 percent were male. Of 403 patients, 33 (8.2%) had HBV co-infection. Prevalence of HBV co-infection in patients who were receiving ART at the time of screening group was 6.1 percent, while patients without ART at the screening time was 11.4 percent. Based on 3TC use at the time of screening, the prevalence in patients receiving 3TC was 6.1 percent whereas patients not receiving 3TC was 10.9 percent.

When patients were categorized into those with and without HBV co-infection. There were no

differences in gender, age and route of transmission between the two groups (Table 1). The results of liver function tests at the study period were not different between the two groups (Table 2). Regarding the results of previous liver function test prior to the initiation of ART, only aspartate transaminase (AST) was significantly higher in patients with HBV co-infection (median, 33 U/L vs. 29 U/L; $p = 0.023$).

The median (IQR) CD4 cell count was 395 (277-555) cells/mm³. Of 403 patients, 372 (92.3%) were

receiving ART and 307 of these (82.5%) had undetectable HIV-1 RNA (<50 copies/mL). The proportion of patients with undetectable HIV-1 RNA was significantly higher in patients without HBV co-infection ($p = 0.046$, Table 1). Of 372 patients receiving ART, 311 (83.6%) received non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen and 3TC was used in the ART regimen in 365 (98.1%) patients. There was a trend toward higher proportion of 3TC use ($p = 0.076$) in patients without HBV co-infection

Table 1. Baseline characteristics between the patients with and without HBV co-infection.

Characteristics	Positive HBsAg (n=33)	Negative HBsAg (n=370)	p value
Gender, number (%)			0.272
- male	23 (69.7)	220 (59.5)	
- female	10 (30.3)	150 (40.5)	
Age, years, mean \pm SD	42.8 \pm 7.7	42.2 \pm 10.0	0.462
Risk of HIV transmission, number (%)			0.461
- homosexual	1 (3.0)	7 (1.9)	
- heterosexual	30 (91.0)	353 (95.4)	
- IVDU	2 (6.0)	9 (2.4)	
- blood transfusion	0	1 (0.3)	
Duration of known HIV-1 infection, months, median (IQR)	57.1 (27.0-104.5)	69.3 (36.4-109.5)	0.261
Receiving ART, number (%)	30 (90.9%)	342 (92.4%)	0.305
Duration of ART, months, median, (IQR) (n=372)	46.9 (24.1-77.3)	56.5 (31.1-85.6)	0.160
ART regimen, number (%) (n=372)			0.822
- NNRTI	24 (80.0)	287 (83.9)	
- PI	6 (20.0)	55 (16.1)	
3TC use, number (%) (n=372)	29 (87.9)	336 (98.2)	0.076
Duration of 3TC use, months, median (IQR), (n=365)	44.6 (24.2-74.0)	51.9 (26.0-75.0)	0.410
CD4 cell count, cells/mm ³	366 (270-487)	398 (278-557)	0.303
CD4 percent, %	17 (14-22)	18 (14-23)	0.941
Undetectable HIV-1 RNA, number (%) (n=372)	19 (63.3)	288 (84.2)	0.046

Table 2. Liver function test between the patients with and without HBV co-infection.

Liver function test, median (IQR)	Positive HBsAg (n=33)	Negative HBsAg (n=370)	p value
Prior to ART initiation			
AST, U/L	33 (27-63)	29 (21-44)	0.023
ALT, U/L	50 (35-83)	41 (32-64)	0.121
ALP, U/L	83 (64-113)	86 (69-164)	0.635
Total protein, g/L	85.1 (79-91.6)	83.6 (78.8-88.1)	0.404
Total bilirubin, mg/dL	0.5 (0.3-0.7)	0.4 (0.3-0.6)	0.337
Direct bilirubin, mg/dL	0.2 (0.2-0.3)	0.2 (0.1-0.2)	0.124
GGT, U/L	88 (44-136)	74 (35-155)	0.446
At study period			
AST, U/L	25 (22-48)	26 (20-36)	0.142
ALT, U/L	49 (37-64)	45 (35-64)	0.985
ALP, U/L	103 (80-151)	96 (70-118)	0.064
Total bilirubin, g/L	81.1 (77.7-84.5)	80.8 (76.1-85.2)	0.834
Total bilirubin, mg/dL	0.4 (0.3-0.6)	0.5 (0.3-0.6)	0.758
Direct bilirubin, mg/dL	0.2 (0.2-0.3)	0.2 (0.2-0.3)	0.174
GGT, U/L	103 (63-169)	86 (55-167)	0.479

AST=aspartate transaminase, ALT=alanine transaminase, ALP=alkaline phosphatase,

GGT= gamma glutamyl transpeptidase

(Table 1). From multivariate analysis, the previous AST level prior to the initiation of ART [odd ratio (OR) 1.020; 95 percent confidence interval (CI), 1.007-1.034; $p = 0.003$] and undetectable HIV-1 RNA [OR 0.243; 95%CI, 0.068-0.870; $p = 0.030$] were significantly associated with the results of screening for HBV co-infection (Table 3).

DISCUSSION

The results from the present study had shown that the overall prevalence of HBV infection in HIV-1 infected Thai patients was 8.2 percent. This prevalence basically remains unchanged from the prevalence of 8.7

percent in a previous study in 2003 in the same institute.⁴ However, according to the subgroups based on receiving ART and 3TC at the screening time, the prevalence was lower in the patients receiving ART and 3TC when compared to the prevalence in patients without ART and not receiving 3TC. Multivariate analysis showed that receiving 3TC prior to HBsAg screening had a trend toward a lower prevalence of HBV co-infection ($p=0.076$). A previous study found that 5 of 33 HBV/HIV-1 co-infected patients receiving ART cleared HBsAg and developed antibody to HBsAg (anti-HBs).⁹ Other prospective study found seroconversion of HBsAg to anti-HBs antibody in

Table 3. Multivariate analysis of factors associated with HBV co-infection in HIV-1 infected patients.

Factor	Odd ratio	95% CI	p value
3TC receiving prior to HBsAg screening	0.353	0.112 - 1.113	0.076
AST prior to ART initiation	1.020	1.007 - 1.034	0.003
undetectable HIV-1 RNA	0.243	0.068 - 0.870	0.030
ALP at study period	1.005	0.996 - 1.013	0.294

1 of 19 in HBV/HIV-1 co-infected patients receiving 3TC-containing ART.¹³ This implies that 3TC may effect the HBsAg seroconversion in patients with HBV co-infection who had not been screened for HBV infection prior to initiation of ART with 3TC in the regimen. Owing to a limited number of subjects in this study, more subjects may be needed to evaluate this significant association. Nevertheless, multivariate analysis showed a significant association between undetectable HIV-1 RNA and HBV co-infection, i.e. patients with undetectable HIV-1 RNA had 76 percent lower chance to have HBV co-infection. Thus, patients who achieved undetectable HIV-1 RNA may gain the effect of ART, in which 3TC was contained in the regimen, of the HBsAg seroconversion.

Previous studies found no association between HBV status and HIV-1 virological response following ART.^{6,14-16} While the others found that chronic HBV infected patients had a lower rate of virological success after ART.¹⁷ In the present study, the patients with HBV co-infection had less undetectable HIV-1 RNA compared with the patients without HBV co-infection (63.3% and 84.2% respectively). Although the median duration of ART in patients without HBV is longer (56.5 vs. 46.9 months), there was no statistical significance.

Two studies found that ALT was lower in HBV/HIV-1 co-infected patients.^{18,19} Three studies showed

no difference in ALT and AST in HBV/HIV-1 co-infection.²⁰⁻²² The other studies found HBV/HIV-1 co-infection associated with elevated transaminase.^{14,15} Although AST prior to ART initiation in the present study was significantly associated with HBV co-infection ($p=0.003$), the median of AST in both patients with and without HBV co-infection was within the normal range (33 and 29, respectively). Additionally, there were no differences of ALT prior to ART initiation and both AST and ALT at the time of study between the two groups. Thus, level of AST or ALT at anytime may not be useful to indicate patients who should be suspected for HBV co-infection.

The limitation of this study is that it was a cross-sectional study, which is difficult to identify the consequence of the causes and results. Further long-term prospective study is needed to identify whether the higher undetectable HIV-1 RNA in patients without HBV co-infection is the result of no HBV co-infection or it is the effect of long-term good adherence to ART and causes to HBsAg seroconversion in these patients.

In conclusion, undetectable HIV-1 RNA from receiving ART prior to HBsAg screening had an effect on the results of screening for HBV infection. Screening for HBV co-infection prior to ART initiation should not be omitted in order to identify the exact HBV co-infection without mislead negative test result with

HBsAg seroconversion from 3TC in ART regimen. The level of AST prior to ART initiation was significantly higher in HBV co-infected patients but still within the normal range. The level of transaminases may not be useful to indicate patients who should be suspected for HBV co-infection. Screening for HBV co-infection among HIV-1 infected patients should be more strongly emphasized.

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