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Higher rate of Hepatitis B antigen and antiHBV antibody seroconversion among HIV/chronic hepatitis B co-infection initiating HBV active HAART from Thailand

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INTRODUCTION

- Hepatitis B surface antigen (HBsAg) loss is considered the ideal outcome of chronic hepatitis B virus (HBV) infection.
- HBsAg loss was reported in 12-17% of subjects from a well documented, predominately genotype A or D infected Caucasian HIV/HBV cohort[1,2]on long term tenofovir.
- A prior study found that patients with HBV genotypes A or D are more likely to lose HBsAg[3]
- However, limited data regarding long term HBV treatment outcomes in HIV/HBV co-infection from Asia where HBV genotype C or B is predominant and the majority of patients acquired HBV perinatally.

OBJECTIVE

- We investigated the rate and predictors of HBsAg loss and antiHBs Ab seroconversion among 213 HIV/HBV coinfected patients from Thailand.

METHODS

- Subjects with confirmed chronic HBV infection (HBsAg positive results >6 months apart) were selected from the cohort.
- Serial HBV serology, HBV DNA, quantitative HBsAg and liver biochemistry were performed every 6 months.

RESULTS

- Of 1739 HIV-infected participants with HBsAg tested, 237 subjects were HBsAg positive (13.6%)
- Only 229 subjects had confirmed chronic hepatitis B
- Of 213 HIV/HBV co-infected subjects included in this analysis, 37(17.4 %) had HBsAg loss and 176(82.6%) remained HBsAg positive
- Demographic data of participants with and without HBsAg seroconversion are presented in Table 1
  - Baseline demographic data was comparable between those with and without HBsAg loss, except for duration of ART which was longer for those with HBsAg loss (12 vs 8 yrs)
  - Median duration on ART was 9 (IQR 3-14) years, with 68.5% on ART for >5 years.
  - Median age was 42 (IQR 36 – 48) years, 69% were male.
  - At start of ART, CD4 cell count was 242 (IQR 107-371) cells/ mm^3
  - At the most recent visit, median CD4 cell count was 523 cells/mm^3 , 84% had undetectable HIV RNA,
  - 56% were HBeAg positive and 82.4% had HBV genotype C
  - Median baseline HBV DNA was 7.2 (IQR 3.2-7.5) log IU/mL.
- Overall, 80.2% had HBV DNA <10 IU/mL at the most recent clinic visit.
- Loss rate of HBeAg (for HBeAg positive cases) and HBsAg were 44% and 17.4%, respectively.
- In a median follow-up of 9 years, **the incidence of HBsAg conversion was 2.93(2.13-4.05) per 100 PY. 15/37 patients (40.5%) developed antiHBsAb conversion at a median duration of 163 weeks after ART.**
- Interestingly, out of 37 HIVHBV patients with HBsAg loss, 20 (54.1%) have already had HBsAg seroconversion before tenofovir initiation.
- Of 17 HIVHBV patients with HBsAg loss after tenofovir initiation, median time on tenofovir before conversion was 57 weeks (range: 23-267)
- In multivaiate analysis (Table 2), HBsAg loss was associated with
  - Younger age [hazard ratio:HR 0.94 (95% confidence interval:95% CI 0.89-0.99), p=0.019]
  - Normal ALT after ART [HR 3.16 (95% CI 1.11-9.02)]. (Figure 3)
- In a subgroup with available HBsAg levels (Figure 1 and 2), levels >100 IU/mL [HR 0.02 (95%CI 0.03-0.21), p<0.001] was associated with a lower clearance of HBsAg than those with levels ≤100 IU/mL in adjusted analyses.

Table 1: Demographics for all HIV-HBV co-infected individuals with and without HBsAg seroconversion.

Characteristics	HIV/HBV N=213	HBsAg Loss (N=37)	HBsAg remained N=176	p-value
Male	148 (69.5)	23(62.2)	125(71.0)	
Median (IQR) Age, years	42(36-48)	41(36-50)	42(36-48)	0.61
Risk factors				**0.59**
Heterosexual	**134(62.9)**	**26(70.3)**	**108(61.4)**	
Men having sex with men	**66(31.0)**	**9(24.3)**	**57(32.4)**	
*** Others**	**13(6.1)**	**2(5.4)**	**11(6.3)**	
HCV co-infection	**3/212 (1.4)**	**1/37 (2.7)**	**2/175 (1.1)**	**0.44**
Alcohol consumption, n (%)	**79/166 (47.6)**	**13/33(39.4)**	**66/133 (49.6)**	**0.29**
Duration on ART, Median IQR, years	**9(3-14)**	**12(8-14)**	**8(3-12)**	**0.002**
Duration of ART, n (%)				**0.010**
< 5 years	**67(31.5)**	**5(13.5)**	**62(35.2)**	
≥ 5 years	**146(68.5)**	**32(86.5)**	**114(64.8)**	
Currently on tenofovir	196(92%)	34(91.9)	162 (92.1)	0.98
Duration of tenofovir, years	6.0(2.7-7.8)	6.5(5.2-8.2)	5.7(2.6-7.7)	0.16
Currently on lamivudine or emtricitabine	207(97.2)	35(94.6)	172(97.7)	0.30
Duration of lamivudine or emtricitabine, years	8.2(2.7-11.9)	10.9(8.2-14.3)	7.8(2.5-10.8)	0.0003
HBV genotype, n (%)	N=142	N=27	N=115	0.15
C	89(82.4)	16(76.2)	73(83.9)	
B	13(12.0)	2(9.5)	11(12.6)	
** HBV-DNA $\log_{10}$ IU/ml	7.2(3.2-7.5)	7.3(2.5-7.7)	7.1(3.2-7.5)	0.78
** CD4,cells/mm^3	242(107-371)	217(93-383)	242(113-370)	0.66
** HIV-RNA $\log_{10}$copies/ml	4.4(3.8-4.9)	4.4(2.2-4.8)	4.4(3.8-4.9)	0.80
** ALT, U/L)	41(29-68)	39(23-80)	42(30-68)	0.48
** HBsAg levels, IU/ml	4.2(3.6-4.7)	4.1(3.3-4.7)	4.2(3.7-4.6)	0.99
** HBeAg positive	81/144 (56.3)	17/27 (63.0)	64/177 (54.7)	0.44
Current CD4, cells/mm^3	523(412-722)	508(398-707)	525(415-734)	0.877
Current HIV RNA <50 copies/ml, n(%)	179(84.0)	34 (91.9)	145 (82.4)	0.151
Current Fibrosis score, PKa	5.3(4.4- 6.6)	5.1 (4.8-5.4)	5.3(4.4- 6.6)	0.8198
Diabetes Mellius, n (%)	**37(17.4)**	**10(27.0)**	**27(15.3)**	**0.088**

* Blood products, needle injury/unknown; ** Baseline visit. All data is expressed as median (IQR).

Table 2: Predictor of HBsAg loss by time to event analysis

Characteristics	Univariate HR	(95%CI)	P value	Multivariate HR	(95%CI)	P
Gender						
Female	1.09	(0.56-2.12)	0.810			
Age at HBsAg tested	0.95	(0.9-0.97)	0.039	0.94	(0.89-0.99)	0.019
Baseline HBeAg positive	1.65	(0.75-3.63)	0.213			
Duration on ARV						
>5 years	1.05	(0.52-2.11)	0.900			
Log HBsAg levels	0.38	(0.23-0.63)	**<0.001**			
Baseline HBV DNA						
< 12 IU/ml	1.93	(0.66-5.61)	0.227			
Undetectable HBV DNA at every visit	4.27	(0.92- 19.83)	0.064			
Baseline ALT						
Normal	1.04	(0.48-2.28)	0.912			
ALT at subsequent visit						
Normal	**3.22**	**(1.14-9.15)**	**0.028**	**3.16**	**(1.11-9.02)**	**0.031**
Current alcoholic drinking, N (%)	0.76	(0.38-1.53)	0.439			
HBV genotype						
C or other	1.1	(0.26-4.72)	0.898			
On lamivudine or emtricitabine	1.04	(0.4-2.73)	0.934	1.13	(0.42-2.99)	0.811
Tenofovir containing regimen	0.79	(0.4-1.53)	0.480	0.73	(0.37-1.44)	0.363
Baseline CD4 cell counts	1.0	(0.99-1.00)	0.664			
HIV RNA, copies/ml						
<50	1.48	(0.56-3.95)	0.431			
Current fibrosis score, KPa						
>9.5	2.63	(0.0-24.61)	0.999			
Diabetes mellitus	1.40	(0.68-2.89)	0.367			

Figure 1: Plot of baseline Quantitative HBsAg in those with and without HBsAg loss

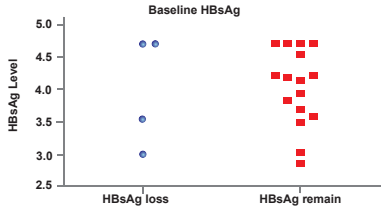


Figure 2: Change in quantitative HBsAg over follow-up

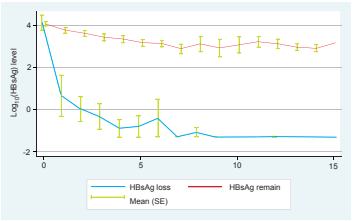
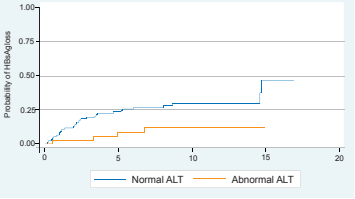


Figure 3: Kaplan-Meier curve of HBsAg loss



DISCUSSION

- Loss of HBsAg is the best measurable indicator for the cure of HBV infection.
- In this study, we demonstrated that 17.4% of our HIV/HBV co-infected individuals lost HBsAg over a median time of 9 years on ART. Our multivariate analysis data was consistent with results from inactive carriers, indicating that age at study entry and normal ALT were associated with HBsAg loss
- More importantly, a lower serum HBsAg level (<100 IU/mL) greatly increased the likelihood of HBsAg loss
- Our prior study has suggested that lower HBsAg level at week12 after ART was associated with HBeAg and HBsAg loss[4]

CONCLUSION

- Rate of HBsAg loss, HBeAg and antiHBsAb seroconverstion in these Asian HIV/HBV co-infected individuals initiating HBV active ART were high.
- Older age and abnormal ALT after ART were associated with reduced HBsAg clearance.
- Our population with HBsAg loss is a promising target for studies exploring intensive biomarkers for potential HBV cure

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