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Hepatitis B Treatment Response to TDF in 3TC-experienced Perinatally HIV-infected Adolescents

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Background

- HIV and Hepatitis B (HBV) coinfection is associated with high risk of progression to chronic liver diseases.
- This is particular concern in perinatally HIV-infected adolescent coinfected with HBV as reactivation of chronic hepatitis might occur in their pubertal years, after immune tolerance phase during the first decade of life.
- According to WHO guideline 2013, tenofovir (TDF) and lamivudine (3TC) or emtricitabine containing antiretroviral regimens are strongly recommended for all HIV/HBV co-infected individuals needing treatment.
- The goal of HBV therapy is to prevent liver disease complications by sustained suppression of HBV replication to the lowest achievable level.

Study objective

1. To describe HBV viral dynamic at 12, 24 and 48 weeks after tenofovir initiation

2. To determine HBV treatment response after treatment with tenofovir and lamivudine-containing combination antiretroviral therapy (cART) regimens

3. To describe rate of hepatitis B envelope antigen (HBeAg) and hepatitis B surface antigen (HBsAg) seroconversion

4. To observe for hepatic flare after adding tenofovir in the cART regimens

Methodology

- A prospective multicenter cohort study was conducted in 4 HIV clinics in Thailand
- Inclusion criterion was HIV-infected adolescents aged 12-25 years coinfected with HBV who have not been treated with TDF.
- The antiretroviral regimen was modified to include both TDF and 3TC.
- Demographic and clinical characteristics were collected at study entry
- Blood specimen was obtained at entry, week 12, 24, and 48.

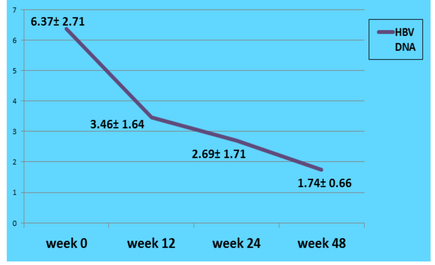
- Laboratory test were performed at the HIVNAT Collaboration laboratory. HBsAg and HBeAg levels were analyzed using semiquantitative method based on the ratio of sample relative light units to a control cut-off (S/CO); hepatitis e antibody (anti-HBe) was measured by Abbott AxSYM, microparticle enzymatic immunoassay; HBV DNA levels were measured by a real-time PCR assay.
- HBV treatment response was defined as undetectable HBV DNA level <200 copies/mL
- Hepatic flare was defined as ALT level increase to > 5 *ULN

Table 1: Characteristic of study participants at study entry (n=12)

Characteristics	Values
Male gender	6 (50)
Current age (yrs)	17.6 (14.2-21.9)
Current weight (kg)	45.3 (33.0-58.0)
Current body mass index (kg/m²)	18.6 (15.1-23.8)
Current CD4 lymphocyte count (cells/mm³)	672 (334-898)
current HIV RNA level < 40 copies/mL	10 (83)
Duration on cART (yrs)	7.5 (2.7-11.9)

Data are in number (%), or median (range) as appropriate
yrs years, kg kilograms, m meter, cART combination antiretroviral therapy

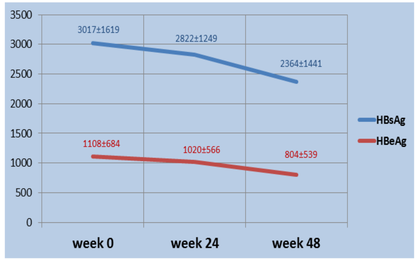
Figure 1: Change in HBV DNA level (log10 copies/mL) after change to combination TDF and 3TC



Results

- From March-October 2012, 12 perinatally HBV/HIV-infected adolescents were enrolled. Their characteristics are shown in Table 1.
- Ten of 12 (83%) has been exposed to 3TC.
- Seven of 8 tested (88%) had HBV-3TC associated mutations (YMDD).

Figure 2: Decline in mean HBsAg and HBeAg titers (S/CO)



Results

- At week 12, 24, and 48 follow-up, significant decreases in HBV DNA and HBeAg levels from baseline value were observed.
- The median HBV DNA reduction from baseline were -2.59, -3.72, and -5.56 $\log_{10}$ copies/mL at week 12, 24, and 48 respectively.
- At the end of follow-up, HBV DNA level were < 200 copies/mL in 78% of cases (the other two had HBV DNA 462 and 473 copies/mL).
- Only a case with DNA-negative at baseline developed HBsAg seroconversion at week 48; however, low-level HBeAg titer persisted, and anti-HBe remained negative.
- Slightly increase ALT was observed, but no statistically or clinical significant; no case experienced hepatic flare.

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Table 1: Treatment response of HBV-HIV-coinfected children after ARV modification to TDF and 3TC-including regimen

Characteristics	week 0	week 12	week 24	week 48	P-value [b]
Number of children [a]	12	12	11	9	
Hepatitis B profile					
HBs Ag positive	12/12 (100)	not done	11/11 (100)	8/9 (88)	
HBsAg level (S/CO)	3017 (1619)		2822 (1249)	2364 (1441)	0.546
HBeAg positive	8/9 (88)		10/11 (91)	7/9(77)	
HBeAg level (S/CO)	1108 (684)		1020 (566)	804 (539)	0.014
anti-HBe positive	1/9 (11)		1/11 (9)	1/9 (11)	
HBV DNA level ($\log_{10}$copies/mL)	6.37 (2.71)	3.46 (1.64)	2.89 (1.71)	1.74 (0.56)	0.018
HBV DNA level <2.0 $\log_{10}$copies/mL	2/12 (17)	3/12(36)	4/11(44)	7/9(77)	
HBV DNA level <20 copies/mL	2/12 (17)	2/12 (24)	2/11 (18)	3/9 (33)	
Liver inflammation					
ALT (U/L)	24 (10-99)	41(14-129)	43 (19-102)	26 (15-86)	0.081
ALT >30 U/L	6/12 (50)	9/12 (75)	9/11 (82)	5/9 (45)	

Data in mean (SD), median (range), or proportion (%) as appropriate; S/CO sample relative light units to a control cut-off (S/CO)
[a] decrease due to 1 missed visit at week 24, 1 lost to follow-up at week 48, and 1 did not reached week 48 due to staggered enrollment
[b] one-way repeated measured ANOVA

Discussion

- The HBV DNA reduction observed in this study was more rapid in the first 12 weeks compared with thereafter, which was similar to previous report in studies among HBV-HIV coinfected adults. [1-3]
- The proportion of cases with HBV DNA suppression (78%) to undetectable level was comparable to those adult studies using TDF with/without 3TC (55-91%).[1-3]
- Low rate of HBsAg and HBeAg seroconversion was observed which might be due to small sample size and short term follow-up.

References
1. Stephan C, Berger A, Carlebach A, et al. Impact of tenofovir-containing antiretroviral therapy on chronic hepatitis B in a cohort co-infected with human immunodeficiency virus. J Antimicrob Chemother 2005;56:1087-93.
2. Matthews GV, Avihingsanon A, Lewin SR, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV coinfected antiretroviral naïve individuals in Thailand. Hepatology 2008;48:1062-9.
3. Lacombe K, Gozlan J, Boelle PY, et al. Long-term hepatitis B virus dynamics in HIV-hepatitis B virus-co-infected patients treated with tenofovir disoproxil fumarate. AIDS 2005;19:907-15.

Conclusions

- HBV DNA suppression was achievable in the majority of adolescents with HBV-HIV coinfection who had been exposed to 3TC, when TDF was added into their pre-existing cART regimen.
- Hepatic flare was not evidenced in this population.
- Long term follow-up is essential to determine whether the efficacy of HBV combination therapy with TDF/3TC sustains or not.