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

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Background

- Hepatitis B virus (HBV) is a common co-infection among HIV-infected individuals in Asia and Africa.
- HIV coinfection has increased risk of HBV disease progression to chronic liver diseases.
- Tenofovir disoproxil fumarate (TDF) has antiviral activities to both HBV and HIV approved for adolescent >12 years in 2010.
- Therefore, many of HIV-HBV co-infected children and adolescents have been exposed to lamivudine monontherapy.

Study Objective

- To determine impact of TDF on kinetics of hepatitis B virus and liver transaminase enzyme in 3TC-experienced perinatally HBV-HIV co-infected adolescents.

Study design

A multi-center prospective cohort in 4 HIV clinics in Thailand

Inclusion criteria

1. HIV-infected adolescents 12-25 years
2. Diagnosed as chronic hepatitis B infection (HBsAg positive > 6 month)
3. Prior exposure to lamivudine

High-level viremia*
HBV DNA > 20,000 IU/mL

Low-level viremia
HBV DNA 60-20,000 IU/mL

Inactive
HBV DNA < 60 IU/mL

Add Tenofovir

Assessments at week 12, 24, and 48	
☑Treatment response of HBV	HBV DNA level, HBsAg, HBeAg
☑ Liver inflammation and hepatic flare	Alanine aminotransferase (ALT) enzyme

* Modified from Lok AS. Hepatology 2007;45:507-39.

Definition of study outcomes

Treatment response of HBV	❑ Change in HBV DNA in $\log_{10}$ IU/mL ❑ Rate of HBV virologic suppression = HBV DNA <60 IU/ml (<300 copies/ml) ❑ Rate of HBeAg seroconversion or HBsAg loss
Liver inflammation and hepatic flare	❑ ALT > 30 IU/mL defined as high ❑ Liver inflammation defined as ALT >3 times ULN ❑ Hepatic flare was defined as ALT >5 times ULN

Laboratory methods

- **HBV DNA levels were measured by a real-time PCR assay (Abbott)**
- **HBsAg, HBeAg were analyzed using ARCHITECT CMIA(Abbott)**

Result: Baseline characteristics

From March 2012 to March 2014, 18 adolescents were enrolled

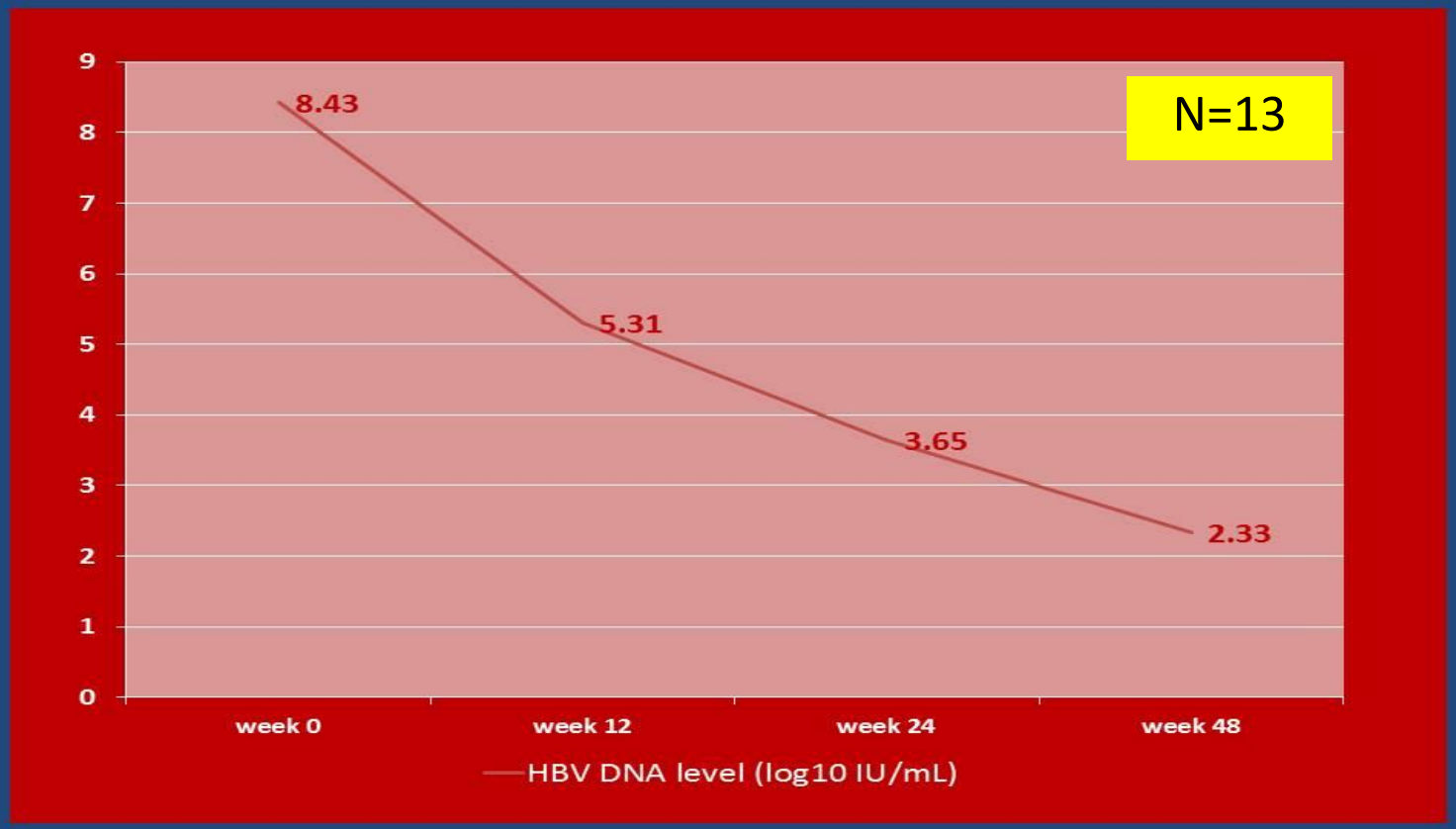
Characteristics	Values
Male	8 (44%)
Age at enrollment (yrs)	17.6 (12.9-21.9)
Body mass index (kg/m^2)	18.6 (15.1-23.8)
CD4 lymphocyte count ($cells/mm^3$)	650 (334-912)
HIV RNA level < 40 copies/mL	15 (83%)
Duration on 3TC exposure (years)	7.3 (0.7-11.1)
Lamivudine resistance associated mutations (YVDD or YIDD)	6/7 (86%)
HBV DNA (log_{10} IU/ml)	7.4 (3.9-8.0)

High HBV viremia (n=13, 72%)

Low HBV viremia (n=3), Inactive stage (n=2)

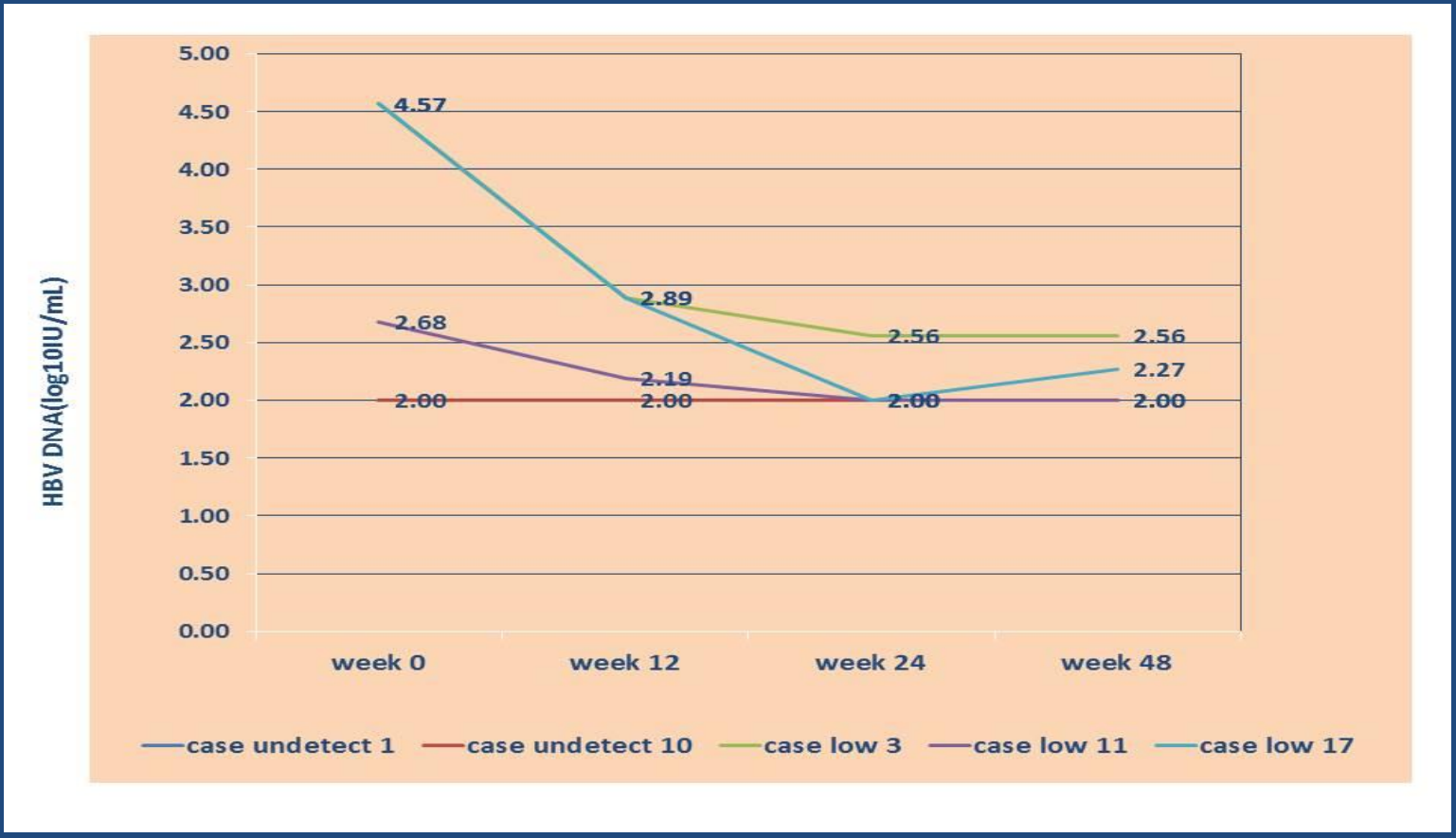
HBV DNA kinetics during 48 weeks among HBV high-level viremia group

At week 48, 7/13 (54%) had HBV DNA level <60 IU/mL
None has HBeAg seroconversion or HBs Ag loss



HBV DNA kinetics during 48 weeks among HBV low-level viremia/inactive carrier

One child with inactive state has HBsAg loss at week 48



ALT change after using TDF

Liver inflammation and hepatic flare in HBV-HIV coinfected adolescents after modification to TDF and 3TC-including regimen (n=18)

Characteristics	week 0	week 12	week 24	week 48
ALT (U/L), median (IQR)	21(13-29)	32(19-61)	37(20-66)	26(20-35)
ALT >30 U/L, number (%)	3(17)[a]	9(50)	10(59)	6(38)
ALT 3-5 *ULN, number (%)	0	1(6)[c]	1(6)	0
ALT > 5 *ULN , number (%)	0	0	0	0

[a] 3 patients with high baseline ALT had persistent elevated ALT up to week 48

[b] ALT > 30 U/L for male, or > 19 U/L for female

[C] 1 patient developed transient elevated ALT (ALT max = 129 U/L)

Discussions: HBV viral suppression

Favorable outcome on HBV viral suppression comparing to adult data

Authors	Population	No. of 3TC exposed	Follow-up duration	Median decline in HBV DNA (log10 copies/mL)	HBV DNA Endpoint (copies/ml)	HBV DNA suppression
Our study	Adolescents (high-viremia)	13/13	48 weeks	-5.9	< 300	54%
	Adolescents	18/18	48 weeks	-5.3		61%
Stephan C.[1]	Adults	20/31	48 weeks	-5.4	< 200	55%
Matthews GV.[2]	Adults	0/11	48 weeks	-4.4	< 170	71%
Lacombe K.[3]	Adults	24/28	71 weeks	-4.6	< 200	75%

[1]J Antimicrob Chemother 2005;56(6):1087-93.
[2]Hepatology 2008;48(4):1062-9
[3]AIDS. 2005;19(9):907-15.

Discussion: HBeAg - HBs Ag loss

- During 1 year of follow-up , only 1 patient had HBs Ag loss.

Authors	Treatment regimen	No. of cases	Follow-up duration	Incidence of HBeAg seroconversion	Incidence of HBsAg loss
Our study	TDF	18	1 year	none	6%
Matthews GV.[1]	TDF/TDF+3TC	23	1 year	31%	9%
Maylin S.[2]	TDF	143	2.5 years	21%	4%
Nunez M.[3]	57% on TDF+3TC	79	4.3 years	28%	13%
Kosi L.[4]	TDF + 3TC or FTC	63	5 years	47%	19%

. [1]Matthews GV. Hepatology 2008;48:1062-9.

[2]Maylin S AIDS. 2012;26:939-49.

[3] Numez M. AIDS Res Hum Retroviruses. 2006 ;22:842-8.

[4]Kosi L. J Viral Hepat. 2012 19:801-10.

Discussion: Risk of hepatic flare

Authors	Follow-up (no. subject)	Hepatic flare (ALT > 5*ULN)	Note
Our study	1 year N=18	Only mild elevated ALT (3-5*ULN = 6%)	Adolescents, 3TC -experienced for 7.3 years Median CD4 cell 650 cell/mm^3
Kosi L.[1]	5 years N=110	2% (2.6-5*ULN = 7%)	Adults with mean baseline CD4 266 cells/mm^3
Matthews GV. [2]	1 year N=36	25%	Adults with advance HIV disease (median CD4 36 cells/mm^3) and concomitant drugs administration

[1]Kosi L. J Viral Hepat. 2012 19:801-10.

[2]Matthews GV. Hepatology 2008;48:1062-9

Conclusions

- Using tenofovir among hepatitis B/HIV co-infected adolescents with 3TC experienced demonstrated favorable outcome **at week 48**

  (61% HBV viral suppression and 6% HBsAg loss)

- None has hepatic flare during 48 weeks of follow-up

- Interval follow up should be done to assess whether patients can achieve goal of HBsAg loss and normalized liver transaminase.

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