International Journal of Pregnancy and Childbirth Vol. 1 (1), pp. 001-007, January, 2015. Available online at www.advancedscholarsjournals.org © Advanced Scholars Journals

Full Length Research Paper

Tenofovir and lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus in highly viremic mothers in Vietnam

Nguyen Van Bang[1], Le Thi Lan Anh[1], Nguyen Thi Van Anh[2], Vu Tuong Van[3], Philippe Halfon[4] and Marc Bourlière[5]

[1]Department of Pediatrics,Hanoi Medical University, Vietnam.
[2]Department of Medical Education/Skills Lab,Hanoi Medical University, Vietnam.
[3]Department of Microbilogy, Machmai Hospital, Vietnam.
[4] AlphaBio Labo, European Hospital, Marseille, France
[5]Department of Gastro-hepatology, Saint Joseph Hospital, Marseille, France.

We evaluated effect and safety of lamivudine and tenofovir in late pregnancy for preventing perinatal transmission of hepatitis B virus (HBV) to infants born to highly viremic mothers. A total of 82 pregnant chronic HBsAg(+) women with high viremia (>10^7 copies/mL) at 32 weeks of gestation were randomly located in 2 groups (lamivudine 100mg or tenofovir 300mg daily for 8 weeks of prepartum to week 4 pospartum). Infants received recombinant HBV vaccine without HBIg and were followed until week 52. We noted a sharp decrease of mean maternal viral load from 5.09 x 10^8 ± 3.19 x 10^8 copies/mL at week 32 of gestation to 1.13 x 10^6 ± 3.91 x 10^6 at labor (*p<0.001*) with 2 undetectable HBV DNA cases (2.4%). The viral load reduction was stronger in tenofovir-treated mothers than in lamivudine-treated ones (*p<0.028*), particularly in 4 $\log_{10}$ reduction (*p<0.001*). At birth, HBsAg was positive in 21/82 (25.6%) and HBV DNA detectable in 7/82 newborns (8.5%). At week 52, HBsAg and HBV DNA was present in serum of 2/82 infants (2.4%). Both tenofovir and lamivudine in late pregnancy showed the same safety and strikingly reduced perinatal transmission of HBV to infants born to highly viremic mothers.

Key Words: Hepatitis B virus, mother-to-child perinatal transmission, highly viremic women, lamivudine, tenofovir; late pregnancy.

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is endemic in some regions, including Asian Pacific where situated Vietnam, with current estimates of 400 million chronically infected individuals worldwide (Elizabeth, 2011); Mahoney, 1999; Sung, 1990; WHO, 2002; Nguyen, 2007). HBV infection early in the life confers a high risk of chronicity, thus establishes entrenched patterns of endemicity because of repeated cycles of mother-to-infant transmission (Dusheiko, 2012; Chen, 2010; Ni, 2010; ACOG, 1993; Jonas, 2009; Umar, 2013; Vransckx, 1999; Wiseman, 2009). In high endemicity regions such as Asia, infants born to mothers positive for both HBsAg and HBeAg have a 70-90% chance of acquiring perinatal HBV infection, and a great majority of them (90-95%) will become chronic HBV carriers (Mahoney, 1999; Dusheiko, 2012; Umar, 2013; Wiseman, 2009). Good practice of vaccination to children born to HBsAg positive women prevents mother-to-child transmission in 80-95% of cases and has critically reduced the incidence of HBV in childhood worlwide (Mahoney, 1999; Chen, 2010; Ni, 2010; Wiseman, 2009). However, estimates of the risk of HBV transmission despite good prophylactic practices vary between 15-25% (Dusheiko, 2012; Wiseman, 2009; Deng, 2012; Han L, 2011; Han GR, 2011; van Nunen, 2000; vanZonneveld, 2003; Li, 2003) and even up to 39% (Xu, 2009). High viral level of HBV in mothers is the most important determinant of this prophylaxis failure (Dusheiko, 2012; ACOG, 1993; Umar, 2013; Wiseman, 2009). Prophylactic therapy during pregnancy is well established and has shown good efficacy in reducing mother-to-infant transmission of HBV and safety for both mothers and babies using lamivudine, telbivudine and recently tenofovir (Dusheiko, 2012; Xu, 2009; Deng, 2012; Han, 2011; Pan, 2012; L, 2003; Tran, 2009). In

*Corresponding author. E-mail: hongbang52@yahoo.com

Vietnam, chronic HBsAg carriage prevalence varies between 10-20% in general population and around 2.7% in children under five despite well conducted active propylaxis against HBV incorporated in national program of vaccination since 1997 (Nguyen, 2007). In the present article, we reported results of a multicenter randomized open-label study evaluating if lamivudine or tenofovir given during late pregnancy to highly viremic mothers could comparatively reduce HBV transmission to their infants, in purpose of searching for a prophylactic agent of first choice in view of cost-effectiveness in public health given large population and high rate of HBV infection in a low-income country.

Subjects and Methods

Eligible subjects included HBsAg positive pregnant women ≥18 years old with an estimated gestational age of 28-30 weeks at screening time and serum HBV DNA≥10^7 copies/mL (CDBAS® AmpliPrep/COBAS® TaqMan® HBV Test, v2.0, Roche Diagnostics, lower limit of detection of 69 copies/mL) in four medical centres in Hanoi (National Hospital of Gynecology and Obstetrics, Hanoi Municipality Hospital of Gynecology and Obstetrics, Bachmai Tertiary University Hospital and International Vietnam-France Hospital in Hanoi). Subjects were excluded if they were co-infected with hepatitis C virus or with HIV or had received any antiviral treatment or had any signs of hepatic, renal or hematologic disorders, abnormal fetal development or gravidic toxemia. Eligibly enrolled pregnant women were randomized (using random table) into two groups, treated from week 32 of gestation to week 4 postartum, by either lamividine (Zeffix®, Glaxo-SmithKline, UK, 100 mg daily) or tenofovir (Gentino®, Standa, Germany, 300 mg daily).

Mothers were seen at week 28 (Screening) and at week 32 (Baseline) of gestation, then every two-week interval until delivery (Birth), finally at week 4 pospartum (Endpoint of treatment) for general and prenatal health checks, treatment observance control and adverse events of drugs under treatment. Their infants were vaccinated with recombinant HBV vaccine (Engerrix-B®, Glaxo-SmithKline) using a standard vaccination schedule of four doses (within 24h of birth, week 4, week 8 and week 48) without HBIg combination. Quantification of HBsAg and HBV DNA levels was performed at a WHO's reference laboratory of Virology Division, Microbiology Department, Bachmai Hospital, using the DNA assay as above-described.

Infants were assessed at birth (within 24h of delivery) and then at every four weeks for the first three months, then every three months and at 52 weeks for physical and mental development and drug adverse events, and for quantitative HBV DNA test (at birth using umbilical cordon blood, then at month 6 and month 12 using venous blood) and other HBV markers at month 6 and month 12 (HBsAg, HBeAg, anti-HBe, anti-HBs and anti-HBc).

All participants signed written informed consent; the study protocol was reviewed and approved by Ethics Committees of Ministry of Technology and Science, of Ministry of Health, of Hanoi Medical Univesity, and of each participating institution.

The primary efficacy endpoints indicated by the rate of HBsAg and/or HBV DNA in children at birth (for HBV intrauterine transmission) and at week 52 (for perinatal transmission). The secondary efficacy endpoints included mean difference (MD) in maternal HBV DNA levels between starting point (Baseline) and at delivery (Birth). Additionally safety measures included adverse events in treated mothers and their infants, death and laboratory abnormalities. These efficacy endpoints were only calculated in completely participated mother-and-child pairs (per protocol). Assuming HBsAg positive rate in infants at week 52 of 10% for treated groups [24] while it was around 40% in untreated (placebo control) as reported by Xu et al in 2008 [22], we planned to enroll 84 subjects to provide >90% power to be able to detect a difference in these proportions at week 52, based upon the one-sided chi-square test at the $\alpha = 0.05$ level.

RESULTS

Between January 2011 and December 2013, amongst 864 chronic HBsAg positive pregnant women (PW), 112 cases (12.96%) were highly viremic (>107 copies/mL), of them 96 (85.7%) signed informed consent to participate in the study and then formed intention-to-study population. Subject disposition and its evolution during follow-up of the study were depicted in Figure 1.

Finally, per-protocol population for analysis consisted of only 82 (85.5%) mother-child pairs who completed the study protocol up to 52 weeks of life of infants; 14 pairs (14.5%) of withrawal (11 pairs) or pending for delivery (3 PW) were excluded from analysis. Characteristics of per-protocol population were presented in Table 1.

There was no difference in characteristics between subpopulations assigned into 2 treated groups with exception of a male predomonance in the group under lamivudine ($p=0.0027$), and more slightly higher rate of cases with adverse events in tenofovir-treated mothers ($p<0.05$). HBeAg positive were in 95.1% of mothers (78/82); there were only 4 HBeAg negative mothers (2 under tenofovir and 2 under lamivudine) in this analysis population.

HBV DNA levels at Baseline (week 32 of gestation) were very high in our study population, with a viral load >108 copies/mL in 71/82 (86.6%) pregnant women. Mean maternal serum HBV DNA was $5.09 \times 10^8 \pm 3.19 \times 10^8$ at baseline reduced to $1.13 \times 10^6 \pm 3.91 \times 10^6$) at Birth (during the labor). The mean HBV DNA reduction after 8 weeks of treatment was then of $5.08.10^8 \pm 3.17.10^8$.

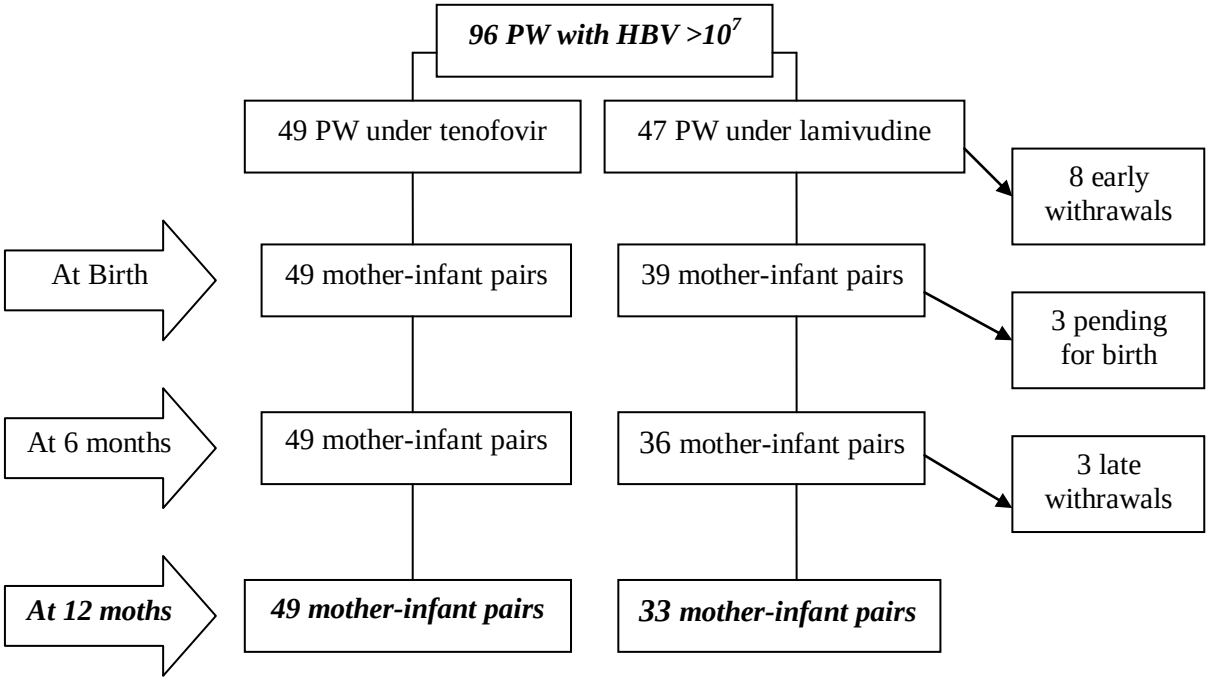

Figure 1. Subject disposition and evolution during follow-up of the study.

Table 1. Characteristics of per-protocol population in the study.

Characteristics	Tenofovir (n=49)	Lamivudine (n=33)	*p*
Mother age in year, mean ± SD (range)	28.8 ± 3.6 (22-44)	28.6 ± 3.9 (22-41)	*>0.05*
Mother HBeAg(+) at week 32, n (%)	48 (98.0)	31 (94.0)	*>0.05*
Mother anti-HBe(+) at week 32, n (%)	1 (2.0)	2 (6.1)	*>0.05*
Mother anti-HBc(+) at week 32, n (%)	49 (100)	33 (100)	*>0.05*
Mother HBV DNA in copies, mean ± SD	$4.98 \pm 3.42.10^8$	$4.86 \pm 3.08.10^8$	*>0.05*
Treatment initiation in week, mean ± SD	31,7 ± 0.5	31.8 ± 0.6	*>0.05*
Treatmen duration in week, mean ± SD	8.4 ± 0.6	8.5 ± 0.5	*>0.05*
Male sex of children, n (%)	19 (33.8)	21 (63.6)	*<0.01*
Weight at birth in kg, mean ± SD (range)	3.2 ± 0.8 (2.7-3.9)	3.3 ± 0.6 (2.6-4.1)	*>0.05*
Cesarian section*, n (%)	11 (22.4)	7 (21.2)	*>0.05*
Breastfeeding, n (%)	45 (91.8)	31 (93.9)	*>0.05*
Mothers with drug adverse events, n (%)	7 (14.3)	3 (9.1)	*<0.05*

** 5 cases with previous cesarean section, 13 cases with prolonged labor*

Mean decrease in $\log_{10}$ of HBV DNA in the tenofovir-treated mothers was significantly stronger than that in the lamivudine-treated mothers (p=0,022). Additionally, at the time of delivery, 2/32 mothers (6.6%), both under lamivudine, had serum undetectable HBV DNA. In addition, HBV DNA levels at the time of delivery remained >106 copies/mL in 12/82 treated mothers (14.6%), of them 10^7 copies/mL in 2 mothers under lamivudine, 10^6 copies/mL in 8 mothers under lamivudine, and in 2 mothers under tenofovir.

In mothers under lamivudine, HBV DNA decrease levels aggregated in 1-3 $\log_{10}$ (25/33 or 75.8%), while in mothers under tenofovir, it aggregated in 3-4 $\log_{10}$ (42/49 or 81.7%). The reduction of HBV DNA levels aggregating in 1-2 $\log_{10}$ was significantly higher in mothers under lamivudinein than mothers under tenofovir (36.4% compared to 4.1% (p<0.01), while HBV DNA reduction aggregating in 4 $\log_{10}$ was far higher in mothers under tenofovir than in mothers under lamivudine (51.1% compared to 15.2%) (p<0.001) (Table 2).

Table 2. HBV DNA reduction levels stratified by log_{10} between Baseline and Birth in mothers under lamivudine and tenofivir.

HBV DNA decrease (log_{10})	Tenofovir (n = 49)	Lamivudine (n = 33)	Total (n = 82)	*p*
Mean ± SD in log_{10}	3.76 ± 0.80	3.06 ± 1.54		*0.022*
1-2 log_{10}, n (%)	2 (4.1)	12 (36.4)	14 (17.1)	*0.008*
3 log_{10}, n (%)	15 (30.6)	13 (39.4)	28 (34.1)	*0.705*
4 log_{10}, n (%)	27 (51.1)	5 (15.2)	32 (39.0)	*<0.001*
5-8 log_{10}, n (%)	5 (10.2)	3 (9.0)	8 (9.8)	*0.480*

Table 3. Serum HBsAg, HBeAg and HBV DNA status at birth, 6 months and 12 months of age in infants born to mothers under either tenofovir or lamivudine.

Serum HBsAg and HBV DNA in infants			Proportions of infants with mothers under treatment			
			Tenofovir (n = 49)	Lamivudine (n = 33)	Total (n = 82)	*p*
At birth	HBsAg	(-)	33 (67.3)	28 (84.8)	61 (74.4)	
		(+)	16 (32.7)	5 (15.2)	21 (25.6)	*0.075*
	HBeAg	(-)	13 (26.5)	10 (30.3)	23 (28.0)	
		(+)	36 (73.5)	23 (69.7)	69 (72.0)	*0.692*
	HBV DNA	(-)	45 (91.8)	30 (90.9)	75 (91.5)	
		(+)	4 (8.2)	3 (9.1)	7 (8.5)	*0.591*
At 6 months of age	HBsAg	(-)	48 (98.0)	33 (100)	81 (98.8)	
		(+)	1 (2.0)	0	1 (1.2)	*NC**
	HBeAg	(-)	45 (91.8)	28 (84.8)	73 (89.0)	
		(+)	4 (8.2)	5 (15.2)	9 (11.0)	*>0.05*
	HBV DNA	(-)	48 (98.0)	33 (100)	81 (98.8)	
		(+)	1 (2.0)	0	1 (1.2)	*NC**
At 12 months of age	HBsAg	(-)	48 (98.0)	32 (97.0)	80 97.4)	
		(+)	1 (2.0)	1 (3.0)[#]	2 (2.4)	*>0.05*
	HBeAg	(-)	47 (95.9)	32 (97.0)	79 (96.3)	
		(+)	2 (4.1)	1 (3.0)	3 (3.7)	*>0.05*
	HBV DNA	(-)	48 (98.0)	32 (97.0)	80 97.4)	
		(+)	1 (2.0)	1 (3.0)[#]	2 (2.4)	*>0.05*

* NC = Not calculated due to “0”effective in box(es), # Horizontal infection case.

The proportions of HBsAg positivity and detectable HBV DNA in umbilical cordon blood of 82 babies born to mothers under either tenofovir or lamivudine were summarized in Table 3. At birth, 16/49 (32.7%) and 4/49 (8.2%) infants of the tenofovir-treated mothers were HBsAg positive and HBV DNA positive compared to 5/33 (15.2%) and 3/33 (9.1%) infants in the lamividine-treated mothers (p = 0.075 and 0.591, respectively). The total positive proportions of HBsAg and HBV DNA at birth in infants of treated mothers were then 21/48 (25.6%) and 7/82 (8.5%), respectively.

At 6 and 12 months of age, 1/49 infants born to mothers under tenofovir with HBV DNA detectable at birth ($2.7x10^2$) remained HBsAg positive and higher levels of HBV DNA (6.4×10^8 and 8.4×10^8 copies/mL, respectively). We noted an additional case with HBsAg positivity and detectable HBV DNA (6.4 x 108 copies/mL) at 12 months. This infant born to a mother under lamivudine had been HBsAg negative and HBV DNA undetectable at birth and at 6 months of age. Therefore, we considered this case as horizontally infected after 6 months of age. At birth, the proportion of infants with HBeAg positive was 69/82 (72.0%) without difference between infants born to mothers under tenofovir and under lamivudine; at 6 months, this proportion decreased to 9/82 infants (11.0%); at 12 months, HBeAg positivity remained persistent in 3/82 infants, including 2 above-mentioned HBsAg positive and HBV DNA positive infants.

The correlation between HBV DNA decrease stratified by log_{10}, in mothers under the antivirals and HBV DNA status in umbilical blood of offspring was presented in Table 4.

In mothers with a viral reduction of 5-8 log_{10}, none of 8 their infants (5 from mothers under tenofovir and 3 from mothers under lamivudine) was HBsAg positive or HBV DNA detectable at birth. Amongst 14 infants born to highly viremic mothers (2 from mothers under tenofovir

Table 4. Correlation between HBV DNA decrease by log_{10}, in mothers under antiviral and HBV DNA status in umbilical blood of offspring.

Decreased HBV DNA in mothers	HBV DNA in cordon blood	Tenofovir n (%)	Lamivudine n (%)	Total n (%)	*p*
1-2 log_{10}, n (%)	(-)	2 (100)	12 (100)	14 (100)	
	(+)	0	0	0	NC*
3 log_{10}, n (%)	(-)	14 (93.3)	11 (84.6)	25 (89.3)	
	(+)	1 (6.7)	2 (15.4)	3 (10.7)	*>0.05*
4 log_{10}, n (%)	(-)	24 (88.9)	4 (80.0)	28 (87.5)	
	(+)	3 (11.1)	1 (20.0)	4 (12.5)	*>0.05*
5-8 log_{10}, n (%)	(-)	5 (100)	3 (100)	8 (100)	
	(+)	0	0	0	NC*

* NC = Not calculated due to “0”effective in box(es).

Table 5. Frequency of clinical adverse events in pregnant women under treatment.

Code Case	3A	15B	29B	35A	43A	51A	56A	61A	67B	83A	Total
Nausea	+	+		+			+			+	5
Fatigue	+	+		+	+	+					5
No appetite	+		+				+				3
Floating	+	+	+								3
Diarrhea		+			+			+			3
Abd pains								+		+	2
Dizziness	+										1
Urticaria									+		1
Itching										+	1
Total	5	4	2	2	2	1	2	2	1	3	24

and 12 from mothers under lamivudine) in whom HBV DNA reduction was slight (1-2 log_{10} copies/mL), none was HBV DNA detectable at birth. Amongst 60 offspring of treated mothers whose viral loads decreased in 3-4 log_{10}, seven were positive HBsAg and detectable HBV DNA at birth, one remained positive at 6 and 12 months (the unique case of perinatal transmission in the study). There was a tendency of higher rate of detectable HBV DNA infants born to mothers under lamivudine than in those born to mothers under tenofovir; however, this tendency did not attain statistical significance ($p>0.05$).

Incidence and frequency of drug adverse events in pregnant women under treatment were described in Table 5.

We observed 24 clinical events occurred in 10 pregnant women under treatment, including 7/49 mothers under tenofovir (14.3%) and 3/33 mothers under lamivudine (9.1%) ($p>0.05$). Most frequent symptoms were nausea and fatigue, followed by loss of appetite, abdominal floating and diarrhea and then abdominal pains. Most of events occurred in the first two weeks of treatment (19/24 events) with a duration <3 days in 4 cases, 3-10 days in 4 cases and 11-21 days in 2 cases. A slight elevation of ALT between 2 to 3 upper limit of normal (ULN) in 2 mothers under tenofovir and to 4 ULN in 1 mother under lamivudine had been noted after 4 weeks of treatment. However, at labor moment, slight elevation of ALT was only noted in a mother under lamivudine. At the endpoint of treatment (4 weeks after delivery), we did not note flare phenomenon in any mother. No significant change in serum creatininemia or hematologic elements had been seen during the treatment. In 82 infants, we did not note any abnormality which might be attributed to adverse events of the drugs on fetuses, newborns or infants.

DISCUSSION

In this study, we evaluated if lamivudine versus tenofovir starting at the week 32 of gestation could comparatively reduce HBV perinatal transmission in infants borns to highly viremic mothers as well as safety profile of these antivirals in pregnant women and their offspring in view of searching a rational and optional regimen for this situation in a low-income nation. Actually, estimates of the risk for mother-to-infant HBV transmission despite vaccination varied and were related mostly to maternal viremia [6,9-16]. Studies suggest that maternal HBV DNA

concentration >108 copies/mL (2.10^7 IU/mL) confers a ≥10% of risk for perinatal transmission despite immunoprophylaxis (Dusheiko, 2012). Further recent data suggest that HBV transmission to infants might not be averted by vaccine prophylaxis alone, but could be prevented by concurrent nucleoside or nucleotide analogue therapy (Dusheiko, 2012; Xu, 2009; Deng, 2012; Han, 201); Pan, 2012; Shi, 2010; van Zonneveld, 2003).

After 8 weeks of treatment using either tenofovir or lamivudine, we noted a remarkable reduction of HBV DNA levels in treated mothers. The mean maternal serum HBV DNA of $5.09 \times 10^8 \pm 3.19 \times 10^8$ at week 32 of gestation reduced to $1.13 \times 10^6 \pm 3.91 \times 10^6$) at the moment of labor ($p<0.001$). The mean HBV DNA reduction was then by $5.08 \times 10^8 \pm 3.17 \times 10^8$, without significant difference between tenofovir and lamivudine-treated groups. When strastified the viral load reduction of HBV DNA in log10, we found that HBV DNA reduction in the tenofovir-treated mothers was significantly stronger than that in the lamivudine-treated mothers. In mothers under lamivudine, HBV DNA reduction aggregated in 1-3 $\log_{10}$ (75.8%), while it was found aggregated in 3-4 $\log_{10}$ (81.7%) in mothers under tenofovir. As a result, the HBV DNA reduction in 1-2 $\log_{10}$ was significantly stronger in mothers under lamivudine than in those under tenofovir, 36.4% compared to 4.1% ($p<0.01$), while the reduction in 4 $\log_{10}$ was far stronger in mothers under tenofovir than in those under lamivudine, 51.1% compared to 15.2% ($p<0.001$). We also noted two cases with undetectable HBV DNA amongst 33 mothers under lamivudine (6.6%). HBV intrauterine transmission, as defined by HBsAg positivity in umbilical cordon blood at birth, was then 21/82 (25.6%). There was a higher tendency of HBsAg positivity in infants born to mothers under tenofovir than those born to mother under lamivudine, 16/49 (32.7%) compared to 5/33 (15.2%); however this tendency was not statistically significant ($p=0.075$). At birth, 7/82 infants (8.5%) were HBV DNA detectable who were among 21 HBsAg positive infants, with 4/49 (8.2%) in infants born to tenofovir-treated mothers and 3/33 (9.1%) in those born to lamividine-treated mothers ($p=0.591$). We also noted that HBV DNA levels in infants were very low at birth. It was <69 copies/mL in 3 cases (1 in tenofovir group and 2 in lamivudine one) and from 69 to 270 copies/mL in 4 infants (1 in lamivudine group and 3 in tenofovir one). Finally, the overall rate of HBV perinatal transmission as defined by serum HBsAg positivity at 52 weeks was of 2.4% (2/82) in this study. In detail, at 6 and 12 months of age, 1/49 infants born to mothers under tenofovir with HBV DNA detectable at birth (2.7×10^2) remained HBsAg positive and HBV DNA detectable (HBV DNA levels of 6.4×10^8 and 8.4×10^8 copies/mL, respectively). The second infant with detectable HBV DNA (6.4×10^8 copies/mL) and positive HBsAg at 12 months of age was born to a lamivudine-treated mother. This infant was HBsAg negative, HBV DNA undetectable at birth and at 6 months, but also unfortunately anti-HBs negative at 6 months. Besid, his father and his elder brother were retrospectively revealed HBsAg positive. Therefore, he was very probably horizontally infected after 6 months of age due to failure for protective antibody production and living in familial environment at very high risk for HBV infection, a very rare and unfortunate event in actual context.

This is the first study on efficacy of prenatal antiviral prophylaxis being carried out in Vietnam. Our results are consistent with other studies conducted in Asia and worldwide (Xu, 2009; Deng, 2012; Han, 2011; Shi, 2010; Su, 2004; Tran, 2009). In a prospective study in China, a total of 151 HBsAg positive women with HBV DNA levels at approximately 10^7 copies/mL, randomly located to receive HBIg (from 28 weeks of gestation until labor), lamivudine (from 28 weeks of gestaion to 4 weeks after birth) or no treatment (control group), Li et al (2003) found a reduction of serum HBV DNA by a mean of 2 $\log_{10}$ in 2 active treatment groups. HBV transmission was reduced by 50% in both the HBIg group (16.1%) and the lamivudine group (16.3%) compared to 32.7% in untreated control group (Li, 2003). In another randomized double blind placebo-controlled study also in China, Xu et al (2009) showed that lamivudine given from week 32 of pregnancy to mothers with HBV DNA concentration of 10^7 copies/mL at baseline had reduced by a mean of 2 $\log_{10}$ copies/mL in the active treatment group, and at 52 weeks of age, 18% of infants born to 56 treated mothers were HBsAg positive, compared to 39% of infants in 26 placebo recipients (Xu, 2009). In another randomized, double blind, placebo controlled study using telbivudine in 190 HBsAg/HBeAg positive mothers with HBV DNA concentration >6 $\log_{10}$ copies/mL at week 20-32 of gestation, Han et al (2010) noted that HBV DNA level decreased from 8.19 $\log_{10}$ copies/mL to 2.35 l $\log_{10}$ copies/mL compared to 7.96 and 7.8 $\log_{10}$ copies/mL in untreated mothers. HBV HBV DNA was undetectable in serum of 30% treated mothers, and HBsAg positive rate at 28 weeks of age was 2.1% in infants born to telbuvidine-treated mothers versus 13% in infants of untreated mothers (Han GR, 2011). In a meta-analysis looking at the efficacy of lamivudine for interruption of mother-to-child transmission of hepatitis B virus from 15 randomized controlled trials, enrolling 1,693 chronic HBV carrier pregnant womens, Han et al (2011) reported an efficacy indicated by HBsAg or HBD DNA of infants at 6-12 months after birth around overall RR of 0.43 (95% CI, 0.25-0.76). The authors also noted that the incidence of adverse effects of lamivudine was not higher in treated women and their offspring than in controll ($p>0.05$), and that the treatment might be only efficient if maternal viral load is reduced to $<10^6$ copies/mL under lamivudine (Deng, 2012)].

In obligation of ethical concerns in human study as well as scarcity of untreated comparative cases for the period of study time, we could not design the untreated control

group to be able to clearly deliniate the part of efficacy of antiviral prophylaxis from the one acting by vaccination. Therefore, the very low rate of perinatal transmission obtained in our study is not easy at all to explicitly explain. Nevertheless, it might be partly results of not only good practice of HBV vaccination in the mass from where come this cohort but also particularly highly sensibility (with a mean HBV DNA reduction of $5.08.10^8 \pm 3.17.10^8$) of wild HBV virus to the drugs treated. As a result of inclusion criteria in our study, all our participants had never been exposured to any antiviral. A part of our study realized in AlphaBio Labo in Marseille (Pr Halfon) did not detect any phenomenon of resistance to lamivudine and tenofovir amongst 29 blood samples from 21 mother whose offspring was HBsAg positive at birth and 8 mothers whose HBV DNA reduction at labour <2 $\log_{10}$). Therefore, the absence of viral resistance to lamivudine and tenofovir evidenced by our study might be another explanation for the very low rate of perinatal transmission of HBV in the present study. This notion of viral resistance to antivirals as well as an exclusion of subjects who were pre-exposured to antivirals did not mention in any study as far as we know.

It is easy to understand that none of 8 their infants born to mothers with a viral reduction of 5-8 $\log_{10}$ was HBsAg positive or HBV DNA detectable at birth. However, it is amazing and difficult to explain why none of 14 infants born to mothers in whom HBV DNA reduction was slight (1-2 $\log_{10}$ copies/mL) was HBV DNA detectable at birth, while amongst 60 offspring of treated mothers whose viral load reduction was strong (3-4 $\log_{10}$ copies/mL), seven were positive HBsAg and detectable HBV DNA at birth, then one remained positive at 6 and 12 months (the unique case of perinatal transmission in the study). Furthermore, although HBV DNA levels at the time of delivery remained 10^6 copies/mL in 12/82 treated mothers (14.6%) (10 under lamivudine and 2 under tenofovir), all offspring of these mothers with modest viral load reduction were intact at week 52, while in the unique HBV perinal infection case, the baseline maternal viral load was $>6.4 \times 10^8$ copies/mL reducing to 5.82×10^5 copies/mL at labor under tenofovir treatment. We supposed that this infant might very probably be already infected by HBV before treatment initiation, either via placenta or even by the presence of hepatitis B virus in oocytes and embryos as reported by Nie et al (2011) (Nie, 2011). This hypothesis is not easy to prove and needs further evidence in the future.

No major safety concerns was noted either in mothers during treatment in late pregnancy or in their fetuses at birth and in infants for 52 weeks of following-up in our study. The safety of lamividine during late pregnacy has been reported in several studies (Xu, 2009; Shi, 2010; Su, 2004); Tran, 2909). For tenofovir, a recent antiviral drug classified as Food and Drug Administration (FDA) pregnancy risk category B, based on data collected in human exposure from 606 pregnant women in the first trimester and 336 in the second trimester showing an associated rate of birth defects ranging from 1.5% (second-trimester use) to 2.3% (first-trimester use) (Tran, 2009), which were completely similar to the background rate (Dusheiko, 2009); Tran, 2009); Antiretroviral Registry, 2008). Tenofovir is very recently recommended by FDA for use in HBsAg positive pregnant women who suffer from serious liver underlying diseases (active hepatitis, hepatic cirrhosis) or who expect to breastfeed their babies or to continue antiviral therapy after delivery Dusheiko, 2009); Tran, 2009). As a result, a few clinical trials in term of preventing HBV perinatal transmission in highly viremic mothers are not accomplished yet for the moment. Our study is, therefore, one of the first trials using tenofovir in pregnant women to prevent HBV perinatal transmission in highly viremic mothers with results of high efficacy and good safety reported.

CONCLUSION

Through this first study dealing with HBV perinatal prevention using antiviral prophylactic therapy in late pregnancy in very highly viremic mothers in the country we found that this strategy might be adequately applicable in daily practice without complication or vicissitude. Our results showed that either lamivudine or tenofovir exhibited a high efficacy in preventing mother-to-child perinatal transmission of HBV and a good safety. However, from the point of view of cost-effectiveness and public health in a low-income country with high endemicity of HBV, a priority for the use of lamivudine in short course with specific purpose of preventing perinatal transmission in highly viremic mothers seemed more explicitly rational in our vision.

ACKNOWLEDGEMENT

The authors deeply thank to (1) Ministry of science and technology (MOST) of Vietnam and French Embassy in Hanoi for approving, sponsoring and following-up for this Lotus project, (2) Ministry of Health (MOH) of Vietnam approving and encouraging the project proposal, (3) Hanoi Medical University (HMU) for ethical approvement and management of the project, (4) Direction Board of 4 participating institutions for their administrative and professional cooperation, (5) AlphaBio Labo of European Hospital in Marrseille for their close collaboration during study, (6) All investigators who recruited patients in this project and Pr Hoang Minh Hang for her input on statistical aspects of the projects.

REFERENCES

ACOG (1993). Hepatitis in pregnancy, Int. J. Gynecol. Obstet. 42: 189-198.

Antiretroviral Pregnancy Registry St eering Committee (2008). Antiretrovital pregnancy reistery international

interim report for 1 January 1989 through 31 July 2008. Wilmington, NC: Registry Coordinating Center, 2008. Antiretroviral Pregnancy Registery Web site.
Chen DS (2010). Toward elimination and eraducation of hepatitis B. J. Gastroenterol. Hepatol., 25(1): 19-25.
Deng M, Zhou X, Gao Sh, Yang SG, Wang B, Chen HZ, Ruan B (2012). The effects of telbivudine in late pregnancy to prevent intrauterine transmission of the hepatitis B virus: a systemic review and meta-analysis. Virol. J., 9: 185. Published on line Sept 4, 2012 doi: 10.1186/1743-442X-9-185.
Dusheiko G (2012). Interruption of mother-to-infant transmission of hepatitis B: time to include selective antiviral prophylaxis? Lancet 379: 2019-2021.
Elizabeth W, Hwang, Cheung R (2011). Global epidemiology of hepatitis B virus infection. North Am. J. Med. Sci., 4(1): 8.
Han GR, Cao MK, Zhao W, Jiang HX, Wang CM, Bai SF, Yue X, Wang GJ, Tang X, Fang ZX (2011). A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J. Hepatol., 55(6): 1215-1221.
Han L, Zhang HW, Xie JX, Zhang Q, Wang HY, Cao GW (2011). A meta-analysis of lamivudine for interruption of mother-to-child transmission of hepatitis B virus. World J. Gastroenterol., 17(38): 4321-4333.
Jonas MM (2009). Hepatitis B and pregnancy: an underestimated issue. Liver Int. 29(Suppl. 1): 133-139.
Li XM, Yang YB, Hou HY, Shi MF, Shen HM, Teng BQ (2003). Interruption of HBV intra-uterine transmission: a clinical study. World J. Gastroenterol., 9(7): 1501-241503.
Mahoney FJ (1999). Update on diagnostic, management, and prevention of hepatitis B virus infection. Clin. Microbiol. Rev. 12(2): 351-366.
Nguyen VT, Mc Laws ML, Dore GJ (2007). Highly endemic hepatitis B infection in rural Vietnam. J. Gasroenterol. Hepatol., 22(12): 2093-100.
Ni YH, Chen DS (2010). Hepatitis B vaccination in children: the Taiwan experience. Pathol. Biol. (Paris) 58(4): 296-300.
Nie R, Jin L, Zhang H, Xu B, Chen W, Zhu G (2011). Presence of hepatitis B virus in oocytes and embryos: a risk of hepatitis B virus transmission during invitro fertilization. Ferlitity and Sterility 95(5): 1667-1671.
Pan CQ, Han GR, Jiang HX, Zhao W, Cao MK, Wang CM, Yue X, Wang GJ (2012). Telbivudine prevents vertical transmission from HBeAg-positive women with chronic hepatitis B. Clin. Gastroenterol. Hepatol., 10(5): 520-526. Kindly avoid the use of et al in this section.
Shi Z, Yang Y, Ma L, Li X, Schreiber A (2010). Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systemic and meta-analysis. Obstet. Gynecol., 116(1): 147-157.
Su GG, Pan KH, Zhao NF, Fang SH, Yang DH, Zhou Y (2004). Efficacy and safety of lamivudine treatment for chronic hepatitis B in pregnancy. World J. Gastroenterol., 10(6): 910-912.
Sung JL (1990). Hepatitis B virus eradication strategy for Asia. Vaccine 8: 95-98.
Tran TT (2009). Management of hepatitis B in pregnancy: Weighing the options. Cleveland Clin. J. Med., 76 (Suppl 3): S25-S29.
Tran TT, Keeffe EB (2008). Management of pregnant hepatitis B patient. Current Hepatitis Reports 7: 12-17.
Umar M, Hamama-Tul-Bushra, Umar S, Khan HA (2013). HBV perinatal transmission. Int. J. Hepatol., 2013:875791. Epub 2013 Apr 22.
Van Nunen AB, de Man RA, Heijtink RA, Niester HGM, Schaml SW (2000). Lamivudine in the last 4 weeks of pregnancy to prevent perinatal transmission in highly viremic chronic hepatitis B patients. J. Hepatol., 32: 1040-1042.
Van Zonneveld M, van Nunen AB, Niesters HGM, de Man RA, Schalm SW, Janssen HLA (2003). Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. J. Viral. Hepatitis 10: 294-297.
Vransckx R, Alisjahbana A, Meheus A (1999). Hepatitis B virus vaccination and antenatal transmission of HBV markers to neonates. J. Viral Hepatitis 6(2): 135-139.
WHO (2002). Hepatitis B. WHO/CDS/CSR/LYO/2002.2: Hepatitis B. http://www.who.int/emc.
Wiseman E, Fraser MA, Holden S, Glass A, Kidson BL, Heron LG, Maley MW, Ayres A, Locarnini SA, Levy MT (2009). Perinatal transmission of hepatitis B virus: an Australian experience. Med. J. Aust., 190(9): 489-492.
Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, Zhang SL, Qiao FY, Campbell F, Chang CN, Gardner S, Atkins M (2009). Lamivudin in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicenter, randomized, double-blind, placebo-controlled study. J. Viral Hepatitis 16: 94-103.