Protocol

Last version

for the study:

Title:

A Maternal Short Course of Tenofovir Disoproxil Fumarate and Infant Vaccine to Prevent Mother-to-Child Transmission of Hepatitis B Virus

Short title:

Antiviral Prophylaxis and Infant Vaccination to Prevent Perinatal Hepatitis B Infection

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Antiviral prophylaxis and infant vaccination to prevent perinatal hepatitis B infection

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Table of Contents

1. Study Title

A maternal short course of tenofovir disoproxil fumarate and infant vaccine to prevent mother-to-child transmission of hepatitis B virus

Short title: Antiviral prophylaxis and infant vaccination to prevent perinatal hepatitis B infection

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3. Project Summary

Full title: A maternal short course of tenofovir disoproxil fumarate and infant vaccine to prevent mother-to-child transmission of hepatitis B virus

Short title: Antiviral prophylaxis and infant vaccination to prevent perinatal hepatitis B infection

Country*:* Thailand and Lao PDR	**Sponsors:** NICHD, IRD

Study centers: 15 sites in Thailand and 9 sites in Lao PDR

Study period: First enrollment: August 2, 2018 Planned enrollment duration: 24 months Primary endpoint available for all participating infants: Fourth quarter 2021 Planned date of last visit completed: May 1, 2022 Biological analyses completed: May 1, 2023 Final report: Fourth quarter 2023	**Clinical Phase***:* Phase III

Primary Objective

To demonstrate that the risk of HBV infection at 6 months of age is lower than 2% in infants who receive active immunization but no HBIg, born to HBeAg positive mothers with satisfactory virological response on tenofovir disoproxil fumarate (TDF) 300 mg per day from 28 weeks gestation to 2 months postpartum.

Secondary Objectives

- To assess pregnancy outcomes, and infant outcomes until 18 months of age.
- To retrospectively determine the risk of transient infection in infants not chronically infected at 18 months of age using anti-HBc antibodies.
- To describe infants' response to HB vaccination in the absence of confounding from HBIg administration, assessed by anti-HBs antibody levels at 1, 2, 4, 6, 12 and 18 months.
- To describe the changes in maternal HBV DNA level from initiation of TDF to delivery.
- To compare the risk of infant HBV infection at 6 months of age with that observed in infants who received HBIg at birth plus HBV vaccine in one of the 2 arms of a previous study conducted in a similar setting in Thailand (iTAP, NCT01745822).
- To assess the risk of transmission in all infants born in the study, including those born to women with unsatisfactory virological response to study treatment.

Design

Prospective multicenter, international (Thailand and Lao PDR), open-label, single arm clinical trial in HBsAg and HBeAg positive pregnant women (from 28 weeks until one year postpartum) and their infants (until 18 months of age).

Planned number of participants

499 women and their infants.

Main inclusion/exclusion criteria

Study Population

Women aged ≥18 years, positive for HBsAg and HBeAg, and negative for HIV antibodies will be proposed to participate in the study.

Women exclusion criteria

- Receipt of antivirals at any time during the previous 9 months.
- Known liver cirrhosis or evidence of hepatocellular carcinoma.
- Creatinine clearance <50 ml/min, calculated using the Cockcroft-Gault formula.
- Confirmed dipstick proteinuria >1+ (>30 mg/dL) or normoglycemic glycosuria

Follow up

Follow-up of women and infants will be carried out on an outpatient basis except for delivery. Study visits for mothers will take place at 28, 32, 36 weeks' gestation, at delivery and 1, 2, 4, 6, and 12 months postpartum. Infant visits are scheduled at birth, 1, 2, 4, 6, 9, 12, and 18 months.

After the beginning of treatment and at the latest at 36 weeks' gestation, virological response to study treatment will be assessed using HBV DNA load measurement. If the level of HBV DNA load has not significantly decreased (at least by 10 fold in IU/mL) and is above 200,000 IU/mL, the site study team will contact the participant to reinforce adherence to study treatment and possibly recommend HBIg administration to the newborn if available.

Infants will receive HB vaccine per national guidelines and their HBV infection status will be assessed at 6 months of age.

Maternal study treatment will be discontinued two months after delivery. However, women with baseline ALT >60 U/L will be assessed for HBV treatment indications before discontinuation during the postpartum period.

Criteria for evaluation/primary endpoint

Primary endpoint: infant HBV infection assessed by the detection of HBsAg at six months of age confirmed by PCR detection of HBV DNA.

Study Treatment

Tenofovir disoproxil fumarate (TDF), one 300 mg tablet once daily from 28 weeks' gestation through two months postpartum.

Statistical considerations

The efficacy of maternal antiviral plus infant vaccine will be assessed based on the upper limit of the 95% Clopper-Pearson confidence interval (CI) of the observed transmission rate. The efficacy of the prevention method will be considered acceptable if the actual risk of transmission is less than 2% in infants born to mothers with satisfactory virological response to study treatment, and who have received HB vaccine but no HBIg.

A sample size of 386 evaluable cases is needed to provide 87% power to demonstrate that the upper 95% confidence interval limit of the risk of transmission is lower than 2% (i.e. the observed risk would be lower than 0.5%). Accounting for 12% unsatisfactory virological response to study treatment at 36 weeks' gestation, and 12% unevaluable cases, 499 women will be enrolled in the study.

In practice, if 4 infections are observed at any time among (386 or less) infants born to mothers with satisfactory virological response to study treatment, the new method would be considered inferior to infant vaccine + HBIg administration. If this was observed before the final analysis, a review by the Data and Safety Monitoring Board would be organized for recommendations, including possible termination of the trial.

4. Background information

4.1 Background

Hepatitis B virus (HBV) infection is the 10th leading cause of death worldwide (1), and hepatocellular carcinoma (HCC), a major complication of this infection, is the 3rd leading cause of cancer death worldwide (2). Pregnant women with chronic HBV infection, as defined by persistence of hepatitis B surface antigen (HBsAg), may have a 30%-40% risk of transmitting HBV to their infants in the absence of any preventative intervention (3–5). Among HBV infected infants, 65-90% will develop the chronic form of the disease (6–9) and will be at risk of developing cirrhosis and hepatocellular carcinoma (HCC) during adulthood (10,11).

HB immunization is highly efficacious in preventing mother-to-child transmission. Wherever universal immunization programs have been implemented, the prevalence of HBsAg in the population has subsequently decreased. Most Asian countries have implemented HBV immunization programs, and coverage has greatly improved within the last 10-15 years (12) but millions of women infected prior to the implementation of immunization programs remain at risk of transmission. Pregnant women with HBeAg, a marker of high viral replication, retain a significant risk of transmitting HBV even when vaccine and HBIg are provided (13,14). Thus, even programs achieving 100% immunoprophylaxis coverage will not be sufficient to achieve HBV eradication.

Efficacy of HB vaccine

Active immunization with HB vaccine is the cornerstone of preventing HBV infection. Several studies have documented that immunization starting with the birth dose can prevent perinatal transmission, including when the mother is HBeAg positive (15). It was estimated that HBV immunization already prevented 210 million new hepatitis B chronic infections by 2015 and will have averted 1.1 million deaths by 2030 (16). The World Health Organisation (WHO) currently recommends HB vaccination of infants regardless of maternal HBV infection status ("universal"), starting at birth, and followed by two injections during the first 6 months of life (17). The timing of vaccination is crucial. Indeed studies have shown that the administration of vaccine cannot cure an infection that is already established (18).

Efficacy of HBIg combined with HB vaccine birth dose

For infants born to HBV infected mothers, the additional administration of HBIg immediately after birth is recommended although this strategy does not prevent all infant infections from mothers with high viremia: in all recent studies where HBIg was administered in addition to vaccine, transmissions. mainly *in utero,* were reported (in randomized studies: 8% (13), 7% (14), and 2% in our recent iTAP study conducted in Thailand (19,20); and up to 11% in a retrospective study in Taiwan (21).

Challenges of universal HBIg provision across diverse clinical settings

Although global coverage with the three doses of hepatitis B vaccine in infancy reached 84% in 2015, coverage with the initial birth dose vaccination is still low at 39% (22), although it seems crucial to prevent perinatal transmission. The concomitant administration of HBIg for neonates born to mothers with high viremia is even more challenging (23) and the 2015 WHO Guidelines noted that HBIg "may not be feasible in most settings" (17). Provision of HBIg to infants born to HBV-infected mothers may not be easy, particularly from a country wide programmatic point of view. A major barrier is the lack of widespread 24/7 availability of HBIg at all maternity units, in relation with several factors: maintenance of refrigerated HBIg stocks, short shelf life, cost considerations, and access to a reliable source of HBIg production from immunized donors. As for all human derived products, there is a theoretical risk of transmission of known or unknown pathogens, although no studies have found any evidence of such transmission. Also, this prevention strategy relies on a single administration of HBIg as soon as possible after birth, heavily dependent on the organization of the maternity team, with no forgiveness if it is not administered within a certain window period. Moreover, delivering vaccine and HBIg is even more complicated when pregnant women deliver at home, often at significant distance from health facilities. While the vaccine can be transported at room temperature, HBIg requires cold chain. For most infants born to women with HBV infection worldwide, the concomitant administration of HBIg will remain probably out of reach for a long time. In Thailand, HBIg administration is recommended to the extent it is available. Practically, HBIg is not available in most hospitals in Thailand (in the iTAP trial, the study coordination directly provided HBIg to sites as HBIg was not available at all sites). In Lao PDR, HBIg is not provided and HBIg is not registered with Health authorities.

Efficacy of maternal antiviral prophylaxis for HBV transmission

The rationale for providing antiviral therapy to highly viremic HBV-infected pregnant women during the last trimester is that the decrease of HBV viremia will provide pre-exposure prophylaxis (i.e. fetal drug exposure through drug crossing the placenta), preventing *in utero* and intrapartum transmission. The effect of tenofovir disoproxil fumarate (TDF) during pregnancy on the risk of infant HBV infection has recently been evaluated in two different randomized clinical trials, one published (14) and one just completed by our research group (24).

In an open-label randomized study conducted by Pan *et al*. in China, pregnant women with chronic HBV infection and high HB viral load received TDF starting from 30-32 weeks pregnancy until one month postpartum, or the standard of care (control group). All infants received HBIg and a first dose of HB vaccine at birth, a second dose of HBIg and vaccine at 2 months of age, and a third dose of vaccine at 24 weeks. There were no HBV infections at 6 months of age in infants born to 92 women who received TDF versus 6 among 88 infants born to women who received the standard of care (p=0.01).

Between 2013 and 2016, PHPT conducted the iTAP study, a multicenter, double-blind, clinical trial in Thailand. HBeAg positive pregnant women with alanine aminotransferase (ALT) ≤60 IU/L were randomized to TDF or placebo from 28 weeks gestation to 2 months postpartum. Infants received HBIg at birth, and HB vaccine at birth, 1, 2, 4 and 6 months. The primary endpoint was HBsAg positivity confirmed by HBV-DNA at 6 months. The sample size was 328 women to ensure 90% power to detect a ≥9% difference in infant HBV infections (based on the assumption that the rate of infection in infants will be 3% in the TDF arm and 12% in the placebo arm). 331 women (168 TDF, 163 placebo) were enrolled. Median age was 26 years, gestational age 28.3 weeks, and HBV DNA 8.0 $\log_{10}$ IU/mL. Of 322 (97%) on-study deliveries, there were 319 singleton, 2 twin pairs and one stillborn (TDF); 21 (7%) (8 TDF, 13 placebo) were preterm. Median time of HBIg and vaccine administration was 1.3 and 1.2 hours after birth, respectively. In primary analysis, 0/147 (0%, 95% CI 0.0-2.5%) infants were infected in TDF versus 3/147 (2.0%, 95%CI 0.4-5.8%, 2 of 3 *in utero*) in placebo (p=0.12). Adverse events did not differ by arm, including maternal ALT ≥300 IU/mL following treatment discontinuation (p=0.29). The study was designed to also determine the timing of infant infection, if any, using infant peripheral blood (as opposed to cord blood) for HBV DNA testing at birth (19,20). A pharmacokinetic substudy of tenofovir was performed among the women randomized to receive TDF. Approximately 10% of the plasma samples collected during the follow-up were found to have undetectable tenofovir concentrations. The pharmacokinetics of tenofovir in women enrolled in iTAP were in the range expected for pregnant and postpartum women receiving TDF alone.

Previous studies have reported higher rates of transmission, up to 12%, when infants born to mother with high viremia received vaccine and HBIg, without maternal antiviral treatment. Medical practices, such as amniocenteses and Cesarean sections, vary across settings and countries, which may account for differences. The unexpectedly low rate of infant HBV infection in the placebo arm of iTAP (HBIg + Vaccine) was consistent with a protective, though incomplete, effect of vaccine and HBIg, compared to 11% (11 of 101) at 9 months in infants born HBeAg positive women in an open label study in Thailand which compared two less intensive vaccine schedules with no HBIg (15). Importantly, in our iTAP study, it was emphasized to the investigators and study personnel that HBIg and vaccine must be administered as soon as possible after birth. This was carefully monitored and any departure from this recommendation prompted immediate review of the case and a corrective action. Indeed, the median time from birth to first vaccination was 1.2 hours (interquartile range: 0.7, 2.2) and only 4% of infants had their vaccine administered more than 4 hours after birth.

Among the HBV infected infants in the placebo arm (HBIg + Vaccine) of our iTAP study:

- Two infants were *in utero* infected (high HBV DNA loads detected since birth), consistent with the hypothesis that HBIg at birth cannot prevent prior *in utero* infection.
- One infant, born by C-section, tested negative for HBsAg and HBV DNA until 4 months of age but was found infected at 6 months. Sequence analysis showed that the virus was almost identical to the mother's virus (one different nucleotide out of 801 bases in the pol region) ruling out a transmission from a third person. Anti-HBs antibody levels decreased after HBIg was administered at birth but there was no increase following vaccination, consistent with the clearance of HBIg and the absence of a successful response to vaccination.

In addition, in another non-randomized study of telbivudine, another potent drug that inhibits HBV replication, versus standard of care, no infants born to mothers who received telbivudine were HBV infected (13).

Safety of maternal antiviral prophylaxis for HBV transmission

In these studies, there were no safety concerns with regard to maternal antiviral prophylaxis, neither for the mothers nor the infants. Some increases of ALT without clinical manifestations were observed. In our iTAP study, 9 (6%) women experienced an ALT ≥300 IU/mL following study treatment discontinuation in the TDF arm versus 5 (3%) in the placebo arm (p=0.29). The proportions of maternal and infant adverse events, pregnancy outcomes and congenital abnormalities were not significantly different between arms. Similarly, a recent meta-analysis by the American Association for the Study of Liver Diseases (AASLD) concluded that the use of TDF during pregnancy appears well tolerated (25).

4.2 Study Rationale

Rationale for not using infant HBIg born to mothers receiving antiviral prophylaxis

Mother-to-child HBV transmission can occur *in utero*, *intrapartum* or in the post-natal period before HB vaccine is effective. If viral particles are transmitted to the infants during the *intrapartum*/early post-natal period, these viral particles can be neutralized by anti-HBs antibodies elicited by immediate vaccination at birth and/or HBIg. However, vaccination and HBIg at birth cannot prevent infections already established *in utero*. In two previous PMTCT of HBV trials (13,14) and the recent iTAP study, no infants were infected when mothers received either TDF or telbivudine during pregnancy, suggesting that a short–course of antiviral treatment during the last trimester and during the early postpartum period can prevent *in utero* transmission, *intrapartum* and early post-natal transmissions. These data support the rationale that the pre-exposure prophylaxis effect of the antiviral transferred to the fetus in utero, and the significant reduction in viral load is sufficient to eliminate the risk of infection before the vaccine elicits an antibody response (i.e. during the 1st month of life). Thus, in the presence of maternal antiviral prophylaxis, it is conceivable to remove HBIg when newborns are vaccinated immediately after birth. The study aims to show that substituting maternal antiviral treatment for infant HBIg can be favorably considered in settings where HBIg plus vaccine has been used as well as in settings where only vaccine is used.

Post-exposure prophylaxis studies conducted in chimpanzees and humans have provided evidence that HB vaccine can prevent infection when administered at the same time or shortly after exposure to HBV:

- In a study investigating the post-exposure effect of vaccination, a first dose of HB vaccine was administered 4, 8, 48, or 72 hours after HBV was inoculated intravenously to 4 chimpanzees (26). A second and a third vaccine doses were administered 2 and 6 weeks after the first dose. Only chimpanzees that received vaccination within 48 hours after HBV exposure (3 of 4 vaccinated) were protected against HBV infection.
- A subsequent set of experiments assessed the protective effect of post-exposure prophylaxis of HB vaccine and/or HBIg. Chimpanzees received immunoprophylaxis (HBIg only or HBIg plus vaccine) simultaneously, 4 hours or 4 weeks after intravenous inoculation of HBV (27). There were no infections when HBIg was administered simultaneously with HBV inoculum, and when HBIg in combination with HB vaccine were administered 4 hours after HBV inoculation. The chimpanzee receiving only HBIg 4 hours after HBV inoculation was infected. Based on these results the authors proposed that “HBIg may be omitted in the post-exposure situation and be replaced by vaccination only”. It was hypothesized that post-exposure hepatitis B vaccination could be effective due to the long incubation period of HBV infection, in the same way as rabies vaccine administered after exposure to the virus.
- In a placebo controlled, randomized, double blind study of the efficacy of HB vaccine conducted among 1,083 homosexual men at high risk of HBV infection in the United States, clinical hepatitis B and subclinical infections occurred less frequently in vaccine than in placebo recipients (1.4-3.4% vs. 18-27%, P <0.0001). Importantly, a significant reduction of HBV incidence was observed within 75 days of randomization, suggesting that HB vaccination remains efficacious even after exposure (28).

Efficacy of maternal antiviral and HB vaccine on mother-to-child transmission of HBV

- In a study analyzing the early viral kinetics of HBV DNA in HBeAg positive patients with chronic hepatitis receiving 12 weeks of either telbivudine, TDF, or both, the mean (SD) reduction in HBV DNA levels in 14 patients on TDF was -4.2 (0.7 log_{10} copies/mL). Each antiviral produced a rapid drop in viral load within the first 2 weeks of treatment (29) (Figure 1).
- In our perinatal study, iTAP, 161 women started TDF at 28 weeks GA with a median HBV DNA load of 8.0 log_{10} IU/mL. At delivery, median HBV DNA load decreased to 3.9 log_{10} IU/mL, i.e. median decrease of 4.00 (IQR 3.16-4.59) log_{10} IU/mL. This decrease is consistent with that observed by Leung *et al*. and that reported in the Pan's study: VL reduction from 8.2 to 4.7 log_{10} IU/mL over a mean of 8.57 weeks of TDF therapy before delivery (14).

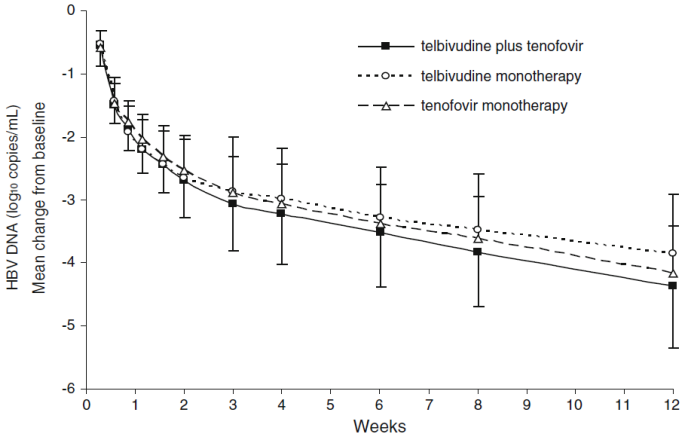


Figure 1: Mean HBV DNA decline over time by treatment group (intent-to-treat population). Error bars are standard deviations. From Leung et al. Infect. Dis Ther (2014) 3:191-202.

In two previous randomized clinical trials, no infections occurred when women received TDF during pregnancy and the newborn received HBIg plus HB vaccine. It is hypothesized that the HB viral load reduction at the time of delivery will ensure a low viral exposure at the time of delivery and HB vaccine given immediately at birth will provide an efficacious post-exposure prophylaxis, even in the absence of HBIg. A meta-analysis showed that there was no additional benefit of HBIg when mothers were HBeAg negative, i.e. with relatively low viral loads (30). Thus, HB vaccine alone may prevent HBV infection if HBeAg positive women receive potent antiviral treatment during pregnancy and achieve a level of HBV DNA similar to that observed in HBeAg negative women.

5. Study specific objectives

5.1 Study objectives

Primary objective

To demonstrate that the risk of HBV infection at 6 months of age is lower than 2% in infants who receive active immunization but no HBIg, born to HBeAg positive mothers with satisfactory virological response on tenofovir disoproxil fumarate (TDF) 300 mg per day from 28 weeks gestation to 2 months postpartum.

Secondary Objectives

- To assess pregnancy outcomes and infant outcomes until 18 months of age.
- To retrospectively determine the risk of transient infection in infants at 18 months of age using anti-HBc antibodies.
- To describe infants' response to HB vaccination in the absence of confounding from HBIg administration assessed by anti-HBs antibodies levels at 1, 2, 4, 6, 12 and 18 months.
- To describe the changes in HBV DNA level from initiation of TDF to delivery.
- To compare the risk of infant HBV infection at 6 months of age with that observed in infants who received HBIg at birth plus HBV vaccine in one of the 2 arms of a previous study conducted in a similar setting in Thailand (iTAP, NCT01745822).
- To assess the risk of transmission in all infants born in the study, including those born to women with unsatisfactory virological response to study treatment.

5.2 Study Design

This study is a multicenter, prospective, open-label, single arm clinical study enrolling HBV chronically infected pregnant women at 28 weeks gestation. Four hundred and ninety-nine (499) women and their infants will be enrolled.

Rationale for important characteristics of the design

Choice of the population. We will select women with HBsAg and HBeAg positive tests. Young pregnant women with HBeAg positive are most likely to have high viremia (median 8 $\log_{10}$ IU/mL in iTAP). The HBeAg test will be used as opposed to HBV DNA load to select pregnant women the most at risk of transmission of HBV to their baby because HBeAg transferred during pregnancy to the infant may play a role facilitating immune tolerance and infection, for consistency with our previous study and because HBeAg tests (Elisa or rapid tests) are widely available, as opposed to HBV DNA measurements, making the study results more generalizable in the future. To characterize the study population, HBV DNA load at enrollment will be retrospectively measured.

Gestational age at treatment initiation. The treatment will start at 28 weeks gestational age based on the obstetrician judgment guided by the review of the date of last menstruation period, physical exam and sonogram. Tenofovir disoproxil fumarate was started between 30 and 32 weeks' gestation in the study by Pan (14) and at 28 weeks +/- 10 days in the iTAP study (24). There were no infant infections in the treated arms of these studies despite slight differences in gestational ages at initiation of treatment.

Evaluation of the response to study treatment at 36 weeks' gestation. In the iTAP study, 12% of women in the TDF arm had HBV DNA at delivery above 200,000 IU/mL, which identifies women at risk of transmission (31). A possible lack of adherence to TDF during pregnancy raises the concern of a subsequent risk of transmission in the absence of HBIg. HBV DNA load will be measured after treatment initiation and at the latest at 36 weeks' gestation to check that HBV DNA load has decreased on study treatment. If the level of HBV DNA load indicates an unsatisfactory response to study treatment, whatever the cause (such as adherence or absorption issues), the site study team will contact the participant to reinforce adherence to study treatment and possibly recommend HBIg administration to the future infant if available.

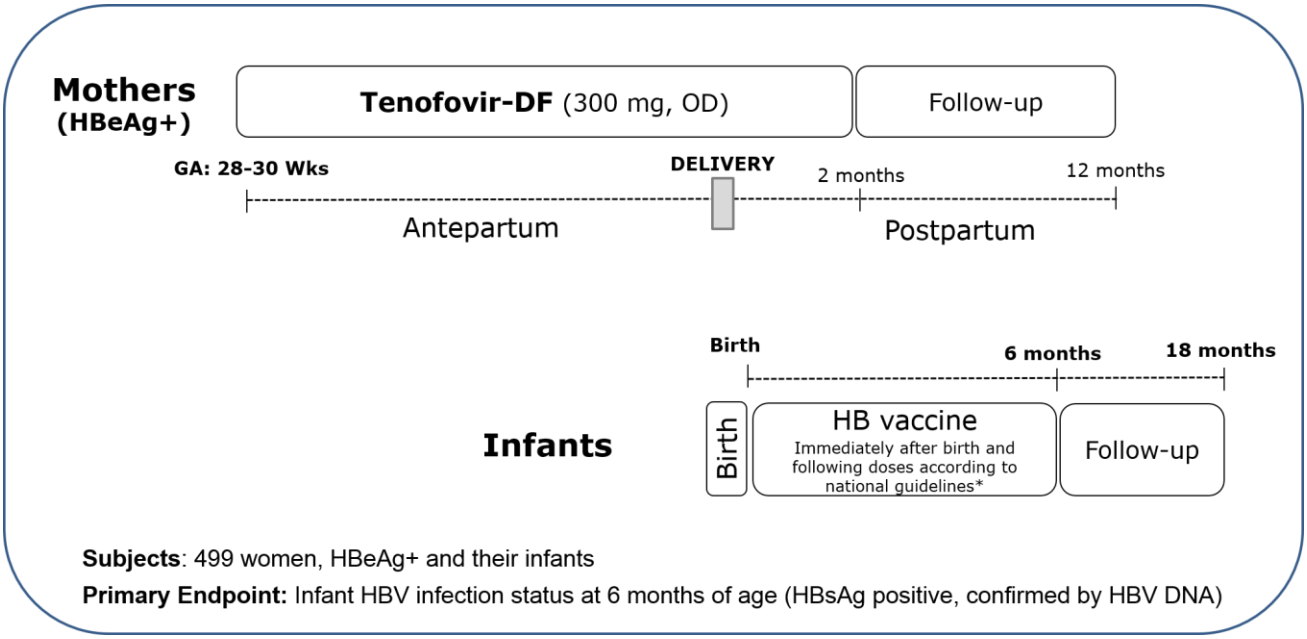
Duration of maternal study treatment. There were variations in postpartum duration of treatment in previous studies and TDF was not discontinued as planned during the postpartum period in several studies. In this study, TDF will be discontinued at 2 months postpartum for all women with baseline ALT ≤60 U/L. For women with ALT >60 U/L, indications for lifelong antiviral treatment will be assessed before postpartum discontinuation of antiviral treatment. TDF is available in Thailand and Lao PDR for treatment of HBV.

Breastfeeding. Mothers will receive study treatment for 2 months postpartum and breastfeed, as recommended by WHO (based on studies finding similar rates of HBV infection in breastfed compared to bottle fed children). The oral prodrug TDF was developed because of the poor bioavailability of oral tenofovir. It is absorbed and converted into the active form, tenofovir, which circulates in the bloodstream. The tenofovir form is excreted in the breast milk and is poorly absorbed by the infant. It was estimated that the infant receives 0.03% of the proposed dose for neonates through breast milk (32).

Diagnosis of HBV infection in infants. The endpoint for this study will be HBV infection at 6 months of age ascertained by HBsAg and confirmed by PCR detection of plasma HBV DNA. Neither the time of contamination nor the time to detection of HBsAg in the fetus/infant serum is known: infant peripheral blood will be drawn for HBsAg test at 1, 2, 4, 6, 9, 12, 18 months (before vaccine administration if at the same date) and, if HBsAg positive, HBV DNA PCR will be performed retrospectively at other time points to determine the timing of infection and chronicity (late infections during infancy are more likely to resolve than if occurring soon after birth).

Evaluation of anti-HBc antibodies at 18 months of age. Antibodies directed against HB core (anti-HBc antibodies) are produced during infection and persist after resolution for at least one year (33). They are used as markers of resolved/prior infection. All infants negative for HBsAg at 18 months of age will be tested for anti-HBc antibodies and, if positive, previous samples will be tested by PCR for HBV DNA to determine whether they experienced a resolved transient HBV infection (i.e. such children

would have been infected but cleared HBV) or have occult HBV infection. Such occult HBV infections may reactivate following the administration of immunosuppressive drugs, for example in the context of chemotherapy for cancer (34).



* HB vaccine schedule in Thailand: at birth, 1, 2, 4, and 6 months
HB vaccine schedule in Lao PDR: at birth, at 6, 10, and 14 weeks

Figure 2: Study design

Women will be followed until 12 months post-partum and children until 18 months of age.

6. Study sites and duration of the study

6.1 Study sites

The list of participating sites is provided in the table below (following the 27 February 2019 and 15 January 2020 amendments, some sites that originally planned to participate did not implement the study and others were added).

Site co-investigators are responsible for the medical management of the patients, the implementation of the study interventions according to the protocol and the completion of the Case Report Forms (CRFs). At each site, the study teams consist of obstetricians, pediatricians, nurses, laboratory technicians, pharmacists and counselors. Each site is regularly monitored by a PHPT clinical research assistant to ensure that study procedures are implemented according to the protocol and regulations.

All study co-investigators and study nurses will be trained before the beginning and during the study on the specific aspects of the study and hepatitis B management and treatment.

Table 1: List of 21 study sites and planned number of participants at each site

Thailand sites	**Province**	**Estimated number of patients to be enrolled**
Health Promotion Center Region 1	Chiang Mai	15
Lamphun Hospital	Lamphun	5
Chiangrai Prachanukroh Hospital	Chiang Rai	30
Chiang Kham Hospital	Phayao	30
Prapokklao Hospital	Chantaburi	5
Banglamung Hospital	Chonburi	5
Chonburi Hospital	Chonburi	6
Nakornping Hospital	Chiang Mai	2
Nopparat Rajathanee Hospital	Bangkok	6
Samutsakhon Hospital	Samutsakhon	20
Samutprakarn Hospital	Samutprakarn	20
Lampang Hospital	Lampang	20
Lao PDR sites		
Mother and child hospital	Vientiane Capital	70
Setthathirath Hospital	Vientiane Capital	45
Mahosot Hospital	Vientiane Capital	65
Champasak Province Hospital	Champasak	40
Savannakhet Province Hospital	Savannakhet	30
Luang Prabang Provincial Hospital	Luang Prabang	15
Xayaboury Province Hospital	Xayaboury	20
103 Hospital	Vientiane Capital	35
Vientiane Provincial Hospital	Vientiane Province	15
Total		499

6.2 Duration of the study

First enrollment: August 2, 2018

Planned enrollment duration: 24 months

Primary endpoint available for all participating infants: Fourth quarter 2021

Planned date of last visit completed: May 1, 2022

Biological analyses completed: May 1, 2023

Final report: Fourth quarter 2023

7. Workplan

7.1 Study population

The population enrolled in the study will be composed of pregnant women meeting all eligibility criteria, and none of the exclusion criteria, and their infants.

7.1.1 Eligibility

- Pregnancy
- Age ≥18 years

- Negative HIV antibody test during current pregnancy
- Positive HBsAg test during current pregnancy
- Positive HBeAg using a rapid test during current pregnancy
- Absence of clinical symptoms of liver disease

7.1.2 Inclusion criteria

Women:

- Meet all eligibility criteria at time of enrollment
- Gestational age of 28 weeks (+/- 7 days) based on the obstetrician judgment guided by the review of the date of last menstruation period.
- Willing and able to provide written informed consent
- Agreeing to bring her infants(s) at the planned study visits at one of the study site until the last visit (18 months after birth) and to inform the site investigators if plans to move to another place and not be able to return to the clinic
- Understand the need for adequate infant immunization for her infant(s) and accept that blood draws will be performed to determine the infant HBV infection status.

Infants:

- All infants born alive to participating mothers can be enrolled in the study.

7.1.3 Exclusion criteria

- Receipt of anti-HBV antivirals at any time during the last 9 months
- Known liver cirrhosis or evidence of hepatocellular carcinoma
- Creatinine clearance <50 ml/min, calculated using the Cockcroft-Gault formula
- Confirmed dipstick proteinuria >1+ (>30 mg/dL) or normoglycemic glycosuria
- Evidence of pre-existing fetal anomalies incompatible with life
- Any concomitant condition or treatment that, in the view of the clinical site investigator, would contraindicate participation or compromise adherence to treatment and satisfactory follow up in the study.

7.1.4 Discontinuation criteria

Women enrolled in the study are free to withdraw their or their infants' participation in the study at any time without jeopardizing their access to standard medical care or possible participation in future research studies.

A study site co-investigator may decide to end a subject's participation in the study if, in his/her own judgment, such participation would be detrimental to the mother or the infant's health or well-being. However, all efforts should be made to inform the study team and discuss options prior such a decision.

The reason for participant discontinuation or withdrawal from the study will be recorded on the "End of Study Form for Women/Child" Case Report Form (CRF).

If a participant fails to return to the clinic for a study visit, the site personnel will attempt to contact the mother and reschedule the missed visit and ascertain whether the participant wishes to continue participating in the study.

Should a participant continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.2 Implementation, data collection, and monitoring procedures

7.2.1 Follow-up and study procedures

1. <u>Women/mothers</u>

The study visits and procedures for women are summarized in Table 2 below.

Eligibility and pre-enrolment tests should be performed prior to enrolment. After enrolment at 28 weeks, maternal visits will be at 32, 36 weeks' gestation, delivery and at 1,2,4,6 and 12 months post-partum.

Table 2. Schedule of visit and study procedures/assessments for mothers

Pregnant Women / Mothers	***Antepartum***					***Postpartum***				
		Study treatment								
	Pre-enrollment	**Enrollment * 28 w.**	**32 w.**	**36 w.**	**Delivery**	**1**	**2**	**4**	**6**	**12**
						months after delivery				
Information about the study, consent process	X	X								
Counseling, Medical exam	X	X	X	X	X	X	X	X		X
Documented telephone contact with the participant									X	
Study treatment dispensation and/or adherence assessment (self-report and pill counts), return of unused study treatment		X	X	X	X	X	X			
Record results of previous HBsAg, HBeAg, HIV and HCV serology and sonogram results		X								
ALT (SGPT), AST (SGOT)[1]		X			X		X	X		
Complete Blood Count		X			X			X		
Serum creatinine[2]		X	X				X			
Dipstick glycosuria and proteinuria		X					X			
HBeAg										X
HBV DNA load		X		X[3]	X					
Tenofovir plasma level[4] (retrospective)				X	X					
Plasma storage		X	X	X	X	X	X	X		X
Cell pellets storage		X								
Total volume blood (mL)		16	10	6	11	4	13	10		8

[1] **APRI score** will be calculated at 4 months postpartum using the formula (AST/ULN) x 100) / platelet count (10^9/L) and **FIB-4** = (age (yr) x AST (IU/L)) / (platelet count (10^9/L) x [ALT (IU/L)$^{1/2}$]).

[2]Creatinine clearance will be calculated using the Cockcroft-Gault formula.

[3]To be measured real-time

[4]To assess adherence in relation to virological response.

* Enrollment can be completed only after transmission to the study coordination center of all relevant information and approval.

All efforts should be made to strictly follow the maternal and infant visit schedule but occasional departures of no more than one week will be considered acceptable.

Women with ALT ≤60 U/L at enrollment will discontinue treatment two months after delivery. Those with ALT >60 U/L will be assessed during the postpartum period for potential long-term treatment indications before discontinuation of study treatment to prevent flares.

With participant's authorization, the study team will record contact information including mobile phone number and address (this information will not be entered in study databases) to be used for contact if needed (e.g. does not show up at a visit).

After the beginning of treatment and at the latest at 36 weeks' gestation, virological response to study treatment will be assessed using HBV DNA load measurement (the date of this assessment should be determined taking into account the risk of premature delivery). If the level of HBV DNA load has not significantly decreased (at least by 10 fold in IU/mL) and is above 200,000 IU/mL, the site study team will contact the participant to reinforce adherence to study treatment.

Expected newborn close contacts. The site study team will explain to the pregnant women that HBV can be transmitted to their infant by close contact with another person infected with HBV and will recommend that they refer any persons who will be in close contact with the infant during at least the first month of infant life for counseling and HBsAg testing. If they agree, the close contacts will be informed of HBV routes of transmission, provided counseling and proposed HBsAg testing.

Management of toxicities will be discussed and reviewed with the site study teams during on-site trainings organized prior to starting the study, and described in detail in the Manual of Onsite Operations. The PHPT coordination center can be reached by fax and e-mail and, if needed, by phone (24/7). At each visit, the study nurse in charge will record the history and the results of the physical exam, record and grade adverse experiences. Women will be asked at all visits to report any concomitant treatments (including use of herbal medicines) or medical interventions. Grade 3 and 4 abnormalities as defined by the NIAID Division of AIDS in the Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July, 2017 will be reported immediately to the PHPT Study Coordination Center. Any serious adverse event, as defined by ICH Good Clinical Practice (GCP) (35), whether or not considered to be related to the study treatment, will be reported within 3 business days to the Study Coordination Center and to national health authorities.

Women with baseline ALT >60 U/L wishing to discontinue the study treatment before 2 months postpartum will be referred to a specialist for hepatitis B infection management.

In case of planned early withdrawal from the study, the investigator will ask for her authorization to perform a last blood draw from her and her infant for safety evaluations and for documentation of the infant's HBV status (see Tables 2 and 3).

All women enrolled in the study will be retrospectively assessed for SARS-CoV-2 antibodies at two time points, at entry in the study, and at the 2 months postpartum visit or before if no sample has been collected at this visit. (2 December 2020 Amendment)

2. Infants

Each infant will have 8 study visits from birth to 18 months of age. The study procedures for the infants are summarized in Table 3, below. Infant peripheral blood will be drawn for HBsAg test at 1, 2, 4, 6, 9, 12, 18 months (before vaccine administration if at the same date). All infants will receive HB vaccine according to national guidelines. In Thailand infants will receive vaccine immediately after birth, then at 1, 2, 4, and 6 months. In Lao PDR infants will receive vaccine immediately after birth, then at 6, 10, and 14 weeks).

Following the assessment of maternal virological response to study treatment, HBIg administration to the newborn may be considered if the level of maternal HBV DNA load had not significantly decreased and was above 200,000 IU/mL.

Table 3. Schedule of visits and study procedures/assessments for infants

Infant assessments	Birth	1 month	2 months	4 months	6 months	9 months	12 months	18 months
Counseling and physical examination	X	X	X	X	X	X	X	X
Record date, time of HBV immunization	X	X	X	X	X			
HBsAg	X[2]	X[1]	X[1]	X[1]	X[1]	X	X	X
HBV DNA PCR	X[2]	X[2]	X[2]	X[2]	X[2]	X	X[2]	X[2]
Anti-HBs antibodies	X	X	X	X	X	X	X	X
Anti-HBc Antibodies								X
Plasma storage (including cord blood)	X	X	X	X	X	X	X	X
Cell pellets storage	X							
Total volume (mL)	4	5	5	5	5	5	5	5

[1] Blood must be drawn before injection of HB vaccine
[2] If HBsAg positive at 6 months

If anti-HBs < 10 IU/L (and HBsAg/HBV DNA negative) at 6, 12 and 18 months of age, the pediatrician in charge will consider revaccination.

7.2.2 Laboratory assessments

7.2.2.1 Sites Assessments

Maternal ALT (SGPT), AST (SGOT), complete blood count, creatinine, and dipstick glycosuria and proteinuria will be tested at each site laboratory using the same procedures as for routine testing. The PHPT laboratory staff will regularly monitor the quality control of the site laboratories.

7.2.2.2 Centralized assessments

The PHPT laboratory (ISO 15189 and 15190 accredited) is responsible for the centralized laboratory exams, virological testing, and samples repository. The blood samples will be stored at the central laboratory for retrospective assessments as needed. It is located in Chiang Mai, under the Faculty of Associated Medical Sciences, Chiang Mai University.

PHPT laboratory will test HBsAg in infant using the Monolisa HBsAg Ultra kit and measure plasma HBV DNA load using the real-time Abbott m2000 system (External quality assurance from Quality Control for Molecular Diagnostics, UK).

HBeAg, anti-HBs antibodies, anti-HBc antibodies and tenofovir plasma level will also be centralized at PHPT laboratory.

For monitoring of virological response in women followed in Lao PDR, HBV DNA concentrations will be measured at Center of Infectiology Lao Christophe Mérieux.

All laboratory procedures will be described in the Manual of Operations.

7.2.3 Data collection

Study data, including data related to adverse events, will be collected at sites by the site investigators or designees. As soon as possible after each visit, the data Manager will run programs to detect data issues that require verification (e.g. inconsistent, missing, unusual or unexpected data) according to specific standard operating procedures.

The following data will be collected for each adverse event: participant identification (including initials, date of birth, gender, weight and height), Adverse Event (AE) Lowest Level Term (LLT) based on the international terminology dictionary *MedDRA*, onset and stop dates, severity, outcome date, assessment of causality with study treatment; date of study treatment first dose and last dose; action taken with study drugs.

Queries will be issued to clarify issues, and confirm or obtain correct information. All data changes will be tracked and documented in compliance with Good Clinical Practice. Study database are backed up daily.

7.2.4 Reporting

<u>Regular study reporting to Ethics Committees</u>

The PHPT data management team will submit every 6 months to Ethics Committees a study progress report that includes:

- Accrual by site
- Participants' characteristics at baseline and follow up study visits
- Participants' follow-up status
- Listing of Serious Adverse Events (SAEs).

<u>Serious Adverse Events reporting</u>

The site investigator or designee will contact the PHPT safety monitors/research nurses or CRA within 24 hours as soon as he/she is aware that a participant is experiencing a SAE.

The PHPT safety monitors/research nurses will assist the site personnel to prepare an SAE report. All information recorded in the SAE report will be checked for consistency with the participant's study records. The Principal Investigator (PI) or a designee physician will then review and sign the SAE report and forward it to the site investigator for validation and signature. The PHPT team will then forward the report to the Ethics Committees, within 3 business days. Further reports will be issued as needed and submitted to Ethics Committees until resolution or stable state.

7.2.5 Study implementation onsite monitoring

Monitoring visits to the study sites will be conducted regularly by PHPT clinical research assistants to review compliance with the protocol, Good Clinical Practice and regulatory requirements. During the first few months of enrollment, the monitoring visits will take place every 2-3 weeks based on the recruitment status of each study site. All activities during visits will be documented and significant issues will be immediately reported to the PHPT Study Monitoring Director.

During these visits, study records will be checked against source documents that site investigators will make available to PHPT team. These documents include but are not limited to informed consent forms,

records related to primary endpoints and safety, regulatory aspects, adverse events, queries, laboratory values. In particular, CRAs will ensure that all events to be reported have been declared to PHPT.

Additional activities include assessing site capacity, appropriate storage and accountability of study drugs, review of screening/recruitment/retention targets, and assessment of the need of additional staff training.

7.3 Study drugs

Tenofovir disoproxil fumarate (TDF) 300 mg tablets. The study site pharmacists will be responsible for study drug storage, dispensation and accountability.

7.4 Biohazard Containment

As the transmission of blood-borne pathogens (including HBV) can occur through contact with contaminated needles, blood, and blood products, appropriate precautions will be used by all personnel when drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the US Centers for Disease Control and Prevention. All infectious specimens will be transported using requirements for shipping infectious substances.

7.5 Statistical considerations

7.5.1 Justifications for the design

Ideally, a design to demonstrate that HBIg can be omitted if mothers receive antiviral (TDF) prophylaxis would be to assess whether this approach is non-inferior to the administration of HBIg in these mothers. As the expected transmission is close to zero, the maximum acceptable difference between the rates of infections resulting from each intervention would be very small. Thus, the sample size needed for such a design would be large (over one thousand), delaying the answer to the research question, limiting drastically the feasibility and the possibility to fund such a study. For example, assuming the actual transmission probability in both arms is 0.5% and a non-inferior transmission probability in the TDF-alone arm is 2% (i.e. a non-inferiority margin of 1.5%), a sample size of 1344 participants would be required to have 90% power using a 2.5% significance level allowing for 12% loss to follow-up.

Several studies have shown that, even if infants received HBIg at birth, infections occurred if mothers were not given antiviral prophylaxis: reported rates of infection were up to 12%. The lowest percentage of infection ever reported in infants receiving vaccine and HBIg was 2%, in the placebo arm of iTAP. Thus, a new strategy reducing the risk of infection below 2% in women with high viremia would be considered as an improvement. Of note, a 2% transmission has also been considered by the WHO as the maximum transmission rate from infected mothers to declare that a member state has virtually eliminated perinatal transmission of HIV. In the case of HBV, only HBV infected women with high viremia are at significant risk of transmission.

7.5.2 Endpoints

<u>Primary endpoint</u>

For this study, infant HBV infection is defined as a positive HBsAg test confirmed by HBV DNA detection by PCR at 6 months of age.

<u>Secondary endpoints</u>

- Occurrence of maternal and infant serious adverse events (ICH SAEs) including DAIDS grade 4 signs and symptoms (36), regardless of their relatedness to the study treatment
- Occurrence of pregnancy outcomes: full term or preterm live births, stillbirths, spontaneous abortions, induced abortions
- Detectable anti-HBc antibodies in children at 18 months of age
- Levels of anti-HBs antibodies in infants at 1, 2, 4, 6, 12 and 18 months
- HBV DNA levels in women at treatment initiation and time of delivery.

- HBV infection status of all infants, including those born to women with unsatisfactory virological response to study treatment

7.5.3 Sample size

The primary objective is to demonstrate that virtually no HBV infection is observed at 6 months of age in infants born to HBeAg positive mothers who receive antiviral prophylaxis from 28 weeks gestation to 2 months postpartum with a satisfactory virological response to treatment. Infants with no infection detected by 6 months of age but found later infected would be considered as experiencing vaccine failure, whatever the cause, and the study team will make all possible efforts to determine the cause of failure.

Thus, for the primary efficacy analysis, the precision of the estimated probability of HBV infection at 6 months of age in infants born to mothers given TDF is crucial.

A significant improvement over the standard HBIg + vaccine strategy would be that adding an antiviral strategy would result to less than 2% transmission. If the true infection rate using the new strategy was 0.5%, a sample size of at least 386 evaluable infants would be needed to demonstrate with at least 87% power that the infection rate using the new strategy is smaller than 2% (see table below).

Table 4. Power to detect a transmission rate significantly lower than 2% with a sample size of 386 evaluable cases according to the actual infection rate (based on the binomial distribution and an exact test with a one-sided significance level of 0.05).

Actual transmission rate	0.3%	0.4%	**0.5%**	0.6%	0.7%	1%
Power	97%	93%	**87%**	80%	71%	46%

Table 5. Precision on transmission rate at 6 months (90% Clopper Pearson exact confidence interval)

Sample size	Observed number of transmissions	%Transmission	90% CI	CI width
300	0	0%	0%,1%	1%
	2	0.67%	0.1%,2.1%	2%
	6	2%	0.9%,3.9%	3%
386	0	0%	0%,0.8%	0.8%
	2	0.52%	0.1%,1.6%	1.5%
	4	1%	0.3%,2.3%	2%
	6	1.6%	0.7%,3.1%	2.4%
450	0	0%	0%,0.7%	0.7%
	2	0.44%	0.1%,1.4%	1.3%
	6	1.3%	0.6%,2.6%	2%

Taking into account 12% non-evaluable cases (including mothers lost to follow up before delivery, stillbirths and infants not assessed for HBV infection at 6 months), as observed in iTAP, a total of 439 pregnant women need to be enrolled to obtain enough evaluable infants.

Infants born to mothers with unsatisfactory virological response at 36 weeks gestation will not be included in the primary efficacy analysis. Assuming that 12% of women will have an unsatisfactory virological response at 36 weeks gestation, a total of **499** pregnant women will be enrolled.

7.5.4 Analyses for the primary objective

The proportion of infants with HBV infection at 6 months of age will be estimated, and the exact 90% CI around this estimate will be calculated based on the Clopper-Pearson method. If the upper bound of the 90% CI is greater than 2% at any time during the study, a DSMB meeting will be convened (See section 7.6 Data and Safety Monitoring Board). The strategy implemented in this study will be considered efficacious if the upper bound of the 90% CI remains lower than 2% throughout the study, i.e. until the primary endpoint for the last evaluable infant is available.

The primary analysis will be conducted as a complete case analysis including infants whose 6 month endpoint is available, regardless of the duration of study treatment the mothers actually received as long as at least one dose was taken. Pregnancies resulting in multiple births (e.g. twins) will be counted as one mother-infant(s) pair, and will be counted as HBV-infected if at least one infant was infected.

Three sensitivity analyses will be conducted: 1) considering infants from multiple pregnancies separately, 2) imputing the last available HBV infection status for infants without 6 month status data, and 3) considering infants with missing data as HBV-infected.

7.5.5 Analyses for the secondary objectives/endpoints

7.5.5.1 Pregnancy/infant outcomes

To assess pregnancy outcomes and infant outcomes until 18 months of age.

The proportion of women with any serious adverse events (ICH SAEs), including DAIDS grade 4 signs and symptoms, from enrollment until study exit will be estimated, and the corresponding 95% CI will be calculated. Time to first SAE will be estimated and plotted using the Kaplan-Meier method. The occurrence of SAEs and time to first SAE in infants will be analyzed in a similar way.

7.5.5.2 Occurrence of pregnancy outcomes: full term or preterm live births, stillbirths, spontaneous abortions, induced abortions

Proportions of women with full term live births, preterm live births, stillbirths, spontaneous abortions and induced abortions, along with their 95% CI, will be provided.

7.5.5.3 Assessment of anti-HBc antibodies in infants at 18 months of age

Retrospective assessment of markers of prior infection (anti-HBc antibodies) in infants at 18 months of age.

The proportion of children with detectable anti-HBc antibodies at 18 months of age will be estimated, and the corresponding 95% CI will be calculated.

7.5.5.4 Infant levels of anti-HBs antibodies

To describe, in the absence of confounding from HBIg administration, the infant levels of anti-HBs antibodies at 1, 2, 4, 6, 12 and 18 months in response to HB vaccination.

Anti-HBs antibody geometric mean concentrations in infants at 1, 2, 4, 6, 12 and 18 months, along with their 95% CI, will be tabulated and presented graphically. Proportions of children with anti-HBs antibody concentrations >10 mIU/mL at each of these time points, along with their 95% CI, will be provided.

7.5.5.5 Maternal HBV DNA changes

To describe the changes in HBV DNA level from initiation of TDF to delivery.

Median (interquartile) change in HBV DNA levels between treatment initiation and delivery will be calculated. The proportion of women with HBV DNA levels >200,000 IU/mL at 36 weeks of gestation will be estimated, and the corresponding 95% CI will be calculated.

7.5.5.6 HBV infection status in all infants

To assess the HBV infection status in all infants, including those born to women with unsatisfactory virological response to study treatment

7.6 Data and Safety Monitoring Board

A Data and Safety Monitoring Board will be appointed to help ensure the safety and interests of the participants; monitor how well the study is being conducted in accordance with the study protocol, and, when needed, suggest changes; assess interim results or external results to determine whether the assumptions (accrual rate, event rate, dropout rate) used to determine the size/length of the study are realistic; monitor efficacy results and suggest whether the study should be modified or terminated; and respond to specific concerns of the study investigators.

The Data and Safety Monitoring Board (DSMB) will be composed of at least 1 hepatologist/ gastroenterologist with a special interest for hepatitis B, 1 pediatrician, 1 obstetrician, 1 infectious diseases specialist, and 1 statistician /epidemiologist, at least 3 of them from South East Asia.

The study will be presented in detail to the DSMB during a protocol initiation review before the study opens. A detailed study monitoring plan, outlining reports on study conduct, will be drafted and presented at this review meeting.

The study will be monitored by the DSMB at least annually. The first DSMB review will be held one year after the first enrollment or earlier when at least 100 pregnant women have been enrolled. This

meeting will allow for the review of the conduct of the study and Adverse Events. Additional DSMB reviews could be triggered if deemed necessary by the Principal Investigator.

In addition, if the number of infant HBV infections reaches 4 at any time, a DSMB meeting will be convened to discuss possible study modifications.

The Study Statisticians, under the supervision of Camlin Tierney, Senior Statistician at the Harvard T.H Chan School of Public Health, Boston MA will prepare the DSMB reports, review data on an interim basis, as well as review the regular progress reports prepared at the Study Coordination Center in Thailand.

In case of premature discontinuation of the clinical trial for any reasons, further management of patients will be organized taking into account DSMB and health authorities advice.

8. Ethical considerations

8.1 Potential Risks to Participants

We hypothesize that the risk of HBV mother-to-child transmission in this study will be lower than 2% (i.e. the upper limit of the 95% confidence interval of the observed rate is less than 2%) because the mothers will receive tenofovir disoproxil fumarate during the last trimester of pregnancy and for two months following delivery and the infants will receive vaccine, starting with the birth dose. No transmission at all was observed in our previous study, iTAP (19,20), in the arm where women received TDF, as well as two other clinical trials evaluating the efficacy of antiviral for PMTCT (37,38). Two percent was the rate observed in the placebo arm of iTAP, the lowest rate ever reported where infants received HBIg and vaccine (and mothers with high viremia received no antivirals). In the proposed study, if more than 3 infections are observed, a DSMB meeting will be immediately convened to review the data and discuss possible adaptations to the intervention or stop the study. If this occurs, enrollment would be halted, all newborns from mothers already enrolled would receive immune globulin until a final decision is made. Any amendment will be submitted to the ethics committee prior to implementation.

In terms of study treatment safety, the risks for the mother and the fetus associated with the use of TDF during pregnancy have been studied in HIV and HIV infected pregnant women and their infants. A systematic review concluded in 2013 that available safety data were generally reassuring for pregnancy outcomes and for lack of congenital or other severe anomalies in exposed infants (19,20).

8.1.1 Maternal risks associated with the use of tenofovir disoproxil fumarate (TDF) during pregnancy

TDF is a nucleotide analogue which inhibits both HIV and HBV replication through inhibition of their reverse transcriptase. TDF is indicated for HIV treatment and HBV treatment, and is part of a WHO recommended drug combination to be started in HIV infected pregnant women after 14 weeks' gestation and continued through the breastfeeding period to prevent mother to child HIV transmission.

In participants with chronic hepatitis B who participated in controlled clinical trials Gilead 0102 and 0103, more participants treated with tenofovir during the 48-week double-blind period experienced nausea (9% versus 3% with adefovir). Other treatment-emergent adverse reactions reported in >5% of participants treated with tenofovir included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash. No significant change in the tolerability profile (nature or severity of adverse reactions) was observed in participants continuing treatment with tenofovir for up to 144 weeks in these studies. Flares have been also observed within the first 4–8 weeks of treatment, accompanied by decreases in HBV DNA levels. No participant had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in therapy (39).

During the course of HBV infection, acute exacerbations of liver damage or hepatic flares can occur spontaneously, be induced by IFN-a therapy or the discontinuation of treatment with nucleos(t)ide analogues. Flares are also observed during induced immune suppression, favoring viral replication. They are most often preceded by high levels of HBV replication and by progressive accumulation of HBV antigens.

Data from iTAP, our previous randomized, placebo-controlled double blind, clinical trial (24) conducted from 2013 to 2016 in a population of pregnant women infected with HBV and their infants confirmed

that there were no significant differences in terms of tolerance and safety among patients assigned to placebo or TDF (19,20).

Three-hundred and thirty-one women (168 TDF, 163 placebo) were enrolled. Median age was 26 years, gestational age 28.3 weeks, and HBV DNA 8.0 $\log_{10}$ IU/mL. Of 322 (97%) on-study deliveries, there were 319 singleton, 2 twin pairs and one stillborn (TDF arm); 21 (7%) (8 TDF, 13 placebo) were preterm. Median time of HBIg and vaccine administration was 1.3 and 1.2 hours after birth, respectively. Forty-one versus 44 women in TDF and placebo, respectively, experienced a grade 3/4 adverse event or ICH SAE. Fifty-five (17%) women had an ALT increase (31 TDF, 24 placebo). Fourteen women (9 TDF, 5 placebo) reached the secondary endpoint of acute exacerbation or flare (ALT >300 U/L) following planned discontinuation of study treatment. ALT >60 U/L at scheduled visits occurred in 157 women (73 TDF, 84 placebo). Monitoring re-tests were systematically conducted. Forty-three versus 38 mother-infant(s) pairs in TDF and placebo, respectively, experienced a grade 3/4 adverse event or ICH SAE. Forty-one (13%) mother infant(s) pairs had jaundice/hyperbilirubinemia (24 TDF, 17 placebo). Infant growth was similar by randomized arm. The vast majority of infants received HBIg at birth and HB vaccines at birth and during infancy as required per protocol.

As in the iTAP study, women will be informed of possible ALT elevations. In case of liver enzyme elevation detected after discontinuation of study treatment, additional tests will be performed for case management and documentation. Expert advice will be sought to consider re-introduction of antiviral therapy in case of significant ALT elevations. Women with high ALT at baseline (> 60 U/L) will be evaluated for chronic HBV treatment indication after delivery and before discontinuation of treatment.

8.1.2 Infant risks associated with the lack of HBIg administration

In two previous randomized clinical trials, no infections occurred when women received TDF during pregnancy and the newborn received HBIg plus HB vaccine. It is hypothesized that the HB viral load reduction at the time of delivery will ensure a low viral exposure at the time of delivery and HB vaccine given immediately at birth will provide an efficacious post-exposure prophylaxis, even in the absence of HBIg. A meta-analysis showed that there was no additional benefit of HBIg when mothers were HBeAg negative, i.e. with relatively low viral loads. Thus, HB vaccine alone may prevent HBV infection if HBeAg positive women receive potent antiviral treatment during pregnancy and achieve a level of HBV DNA similar to that observed in HBeAg negative women, i.e. with low viremia as in women who receive antivirals. Moreover, although HBIg is recommended by the Royal College of Pediatricians, this intervention is not provided for free in the context of the Universal Health Coverage program and most children born to HBV infected mothers do not receive HBIg at birth. Some obstetricians propose the parents to purchase the HBIg at a non-hospital pharmacy at their own expense (US$30 to US$130, depending on manufacturer). In the proposed study all women will receive antiviral until 2 months postpartum, which will reduce the infant exposure to HBV to levels that are not associated with perinatal transmission if the child is vaccinated. In addition, the potential close contacts of the infant will be screened for HBV infection and educated about the risk of transmission to the newborn in the first few weeks of life.

8.1.3 Infant risks associated with in utero exposure to tenofovir

Tenofovir is classified in category B of the US FDA. The data collected in the Antiretroviral in Pregnancy Registry (issued date: June 2017) (40) show that there have been no increase in birth defects in 3229 women exposed during the first trimester and 1480 women during the second and third trimester.

To our knowledge, no cases of mitochondrial toxicity in children exposed to tenofovir in utero have been reported to date. In iTAP study, a check list of signs and conditions suggesting possible mitochondrial dysfunction was completed at the 6 month visit. Data were available for 290 of 294 (99%) infants. One infant (placebo arm) had nystagmus (grade 1, mild). One infant (TDF arm) had persistent anemia and neutropenia reported as a grade 1/2 (mild/moderate) adverse event.

8.2 Adequacy of Protection Against Risks

8.2.1 Recruitment and informed consent

At the clinical sites of the study all co-investigators will receive training on Good Clinical Practice (GCP) and Human Subject Protection prior to the implementation of the study. As for our previous studies, a

specific training for co-investigators, nurses and counselors will be conducted prior to the implementation of the study. Training will address the specific aspects of the study, the GCP requirements, and procedures for protection of human participants in clinical research.

All pregnant women are screened for HBV infection during pregnancy. In this study, women with positive HBsAg and HBeAg tests will receive counseling and comprehensive information about HBV infection, the risk of transmission to their infants and the details of the study. They will then be proposed participation in the study. If available, the infant's father will be informed and asked for consent. Mothers will be enrolled in the study if they consent and meet the selection criteria. If a woman would like her infant receive HBIg, she will not be enrolled in the study.

The consent form will be drafted in English, translated into Thai, discussed, and reviewed by the PHPT Community Advisory Board until the final version translated into Thai and back translated into English to ensure the accuracy of translation. The same process will be followed for Lao translation. The language will be as practical and non-technical as possible to ensure that it is understandable to all study participants. The final consent forms will be submitted to the relevant Ethics Committees. At each site, the co-investigator will thoroughly discuss with each woman and the infant's father if available the information included in the consent. The consent form will describe the purpose of the study, the procedures to be followed and the potential risks and benefits of participation. The consent document will specify the woman's freedom to withdraw her participation or the participation of her baby at any time without compromising access to future medical care. Written informed consent from the father will also be obtained if possible, for the participation of the infant.

The consent form will include the names and contact details of the site co-investigator and an independent physician, whom the study participant may contact with any questions. A copy of the consent document will be given to the participant. In addition, study participants may contact the Clinical Trial Unit, 24 hours a day by phone. The original consent forms will be kept in a locked cabinet at the site. If new information relevant to the participant's consent or her willingness to continue participation in the study becomes available, the participants and potential participants will be informed. Any changes to the consent document will be submitted to the relevant ethics committees.

8.2.2 Protection against risk

8.2.2.1 Institutional Review Board/ Ethics Committees

Prior to the initiation of the study in a country, the protocol and patient consent documents will be submitted for review and approval to ethics committees at national level, and local level if available. Subsequent modifications will be submitted for approval before implementation.

8.2.2.2 Expedited Adverse Experience Reporting

All clinical adverse events and abnormal laboratory values will be recorded and graded. For severe toxicity and serious adverse events, as defined by ICH GCP (35), possibly related to study drugs, a report will be sent to the relevant Ministry of Public Health, within 3 business days of awareness. If a participant dies, events prior to and at the time of death will be transcribed from hospital records, and possible cause(s) of death will be investigated. Management of toxicities and dose modifications for patients will be managed with experts' advice as needed.

8.2.2.3 Confidentiality

Every effort will be made to maintain the confidentiality of the study participants and this will be stressed during Human Subjects Protection training session of study personnel at all sites. To minimize this risk, study participants will not be identified by name on any study documents but by patient identification number. All evaluation forms, laboratory specimens, reports and other records will be identified only by the patient identification number to maintain participant confidentiality. All records will be kept in a locked file cabinet in the clinical research unit. All computer entry and networking programs will be processed with patient identification number only. Clinical information will not be released without the written permission of the patient except when necessary for monitoring by PHPT Study Coordination Center or the sponsors.

8.2.2.4 Compensation

Immediate necessary care is available free of charge to mothers and her infant in the case of medical problems related to participation in this study. However, the study is not responsible for treatments unrelated to the study and no financial compensation will be provided.

8.2.2.5 Other related ethical aspects

The subject information sheet is written in Thai or Lao language, and physician or hospital's names, contact address and telephone number will be specified at each site.

8.3 Potential Benefits of the Proposed Research to the Participants and Others

8.3.1 Mothers

In this study, co-investigators and their teams will closely monitor mothers and infants. The co-investigators will have received specific training on the specific aspects of HBV infection prevention and management and information about tenofovir disoproxil fumarate use during pregnancy for the conduct of the study. As in our previous iTAP study, they will have easy access to national and international experts who are knowledgeable in the management and treatment of HBV disease for any specific questions related to case management.

8.3.2 Expected infant close contacts

The expected close contacts of the infant will be proposed counseling about HBV transmission and HBsAg test. This will not be mandatory for participation in the study but highly recommended. Indeed referring a relative for HBV testing will require that the woman discloses her HBV status, which may be not always desirable. HBV discrimination and stigma is uncommon in Thailand and Laos. If relatives are diagnosed with HBV infection, they will be referred to a gastroenterologist for further follow up and evaluations.

8.3.3 Infants

All infants will receive follow up assessments until 18 months after birth, including diagnosis of HBV status and, if infected, the site pediatrician will provide appropriate counseling and follow up.

The infants will not be exposed to the theoretical risk associated with the use of human derived products, though, to date, the process of HBIg production is considered safe, and no studies have found evidence of transmission of pathogens with HBIg derived from human donor blood.

8.4 Importance of the knowledge to be gained

Despite the use of vaccine and in some cases the addition of HBIg, the risk of perinatal transmission of HBV persists in the study population, most often infected with HBV genotype C (85% in Thailand or Laos), which has a high viral replication rate. Several studies have documented that the use of vaccine, with or without HBIg, cannot prevent all transmissions. However, clinical studies have shown that no perinatal transmissions occurred when antivirals were prescribed to the mother at the end of pregnancy and during the early postpartum period. Antivirals can decrease viral replication to levels similar to that found in women who do not usually transmit the virus if the infant receives vaccine.

It is unlikely that the use of HBIg is useful when mothers have low viral loads, as shown by a systematic review and meta-analysis of the comparative efficacy of vaccine alone or vaccine + HBIg in infants born to mothers with a positive HBsAg test but HBeAg negative test (associated with low viral loads), concluding that "vaccine alone seems to be equally effective to the combination of HBIG and hepatitis B vaccine for neonates of HBsAg+/HBeAg 2 mothers in preventing infection" (30).

Moreover, the provision of HBIg to infants born to HBV-infected mothers can be challenging from a programmatic point of view, a major issue is the lack of widespread availability of HBIg 24/24 7/7 at all maternity units, due to multiple factors: need for a cold chain and the maintenance of a refrigerated stock of HBIg, short shelf life, cost considerations, and reliance for HBIg production on the availability of human plasma from immunized donors not infected by any other pathogens. Also, this prevention strategy relies on a single administration of HBIg as soon as possible after birth, heavily dependent on the organization of the maternity team, with no forgiveness if it is not administered. In several small hospitals in Thailand, it is known that HBIg are usually not available.

The proposed study has been designed to provide clear data on the efficacy of an intervention to decrease HBV perinatal transmission in this population. If such an intervention were proved to be safe and efficacious, recommending and implementing this approach would have a significant public health impact.

9. References

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Appendix 1: Cockcroft-Gault formula for women

$$\frac{(140\text{-age [in years]}) \times \text{weight [in kg]} \times 0.85}{(72 \times \text{creatinine [in mg/dL]})}$$

Calculation on line at: http://nephron.com/cgi-bin/CGSI.cgi

Appendix 2: Amendment dated 19 July 2019

1. In the original protocol it was originally planned to measure the maternal serum concentration of phosphorus and calcium at the visits scheduled at enrollment, 32 weeks of pregnancy, and 2 months postpartum.
   However, current guidelines for the use of tenofovir disoproxil fumarate (TDF) do not recommend systematic measurement of these electrolytes. The TDF/Viread Package Insert of TDF states only that "Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed ***in patients with mild renal impairment***". The new version of the protocol does not require the measurement of phosphorus and calcium because women with renal impairment of any severity cannot be enrolled in the study (normal creatinine clearance, no confirmed normoglycemic glycosuria, no confirmed proteinuria).
   Table 2 has been modified accordingly.

2. The list of “Exempted Congenital Anomalies/Birth Defects (Listed by Body Site)” has been added as an Appendix. These anomalies do not need to be immediately reported to the Ethics Committees but will continue to be recorded in the case report forms.

Appendix 3: Exempted Congenital Anomalies/Birth Defects (19 July 2019 Amendment)

3.1. Listed by Body Site

Abdomen/Groin/Pelvis

Diastasis recti
Hernia, inguinal or umbilical without mention of obstruction or gangrene
Hip click, with no follow-up or therapy
Umbilical artery, single
Umbilical cord atrophy
Urachus, patent

Chest/Thorax

Breast hypertrophy
Inverted nipples
Nipples, anomalies of
Rib, cervical

Face/Mouth

Brushfield Spots
Duct, lacrimal, stenosis, stricture, or obstruction of
Epicanthal folds
Epstein's Pearls
Esotropia
Exotropia
Gum cysts - includes epulis, ranula, mucocele
Macrocheilia (large lips)
Microcheilia (small lips)
Nose, congenital deviation of septum of
Nose, flat bridge of
Nystagmus
Palate, high-arched
Palsy, facial
Protruding tongue
Sclera, blue
Teeth, natal
Tongue tie

Foot/Toe

Foot, rocker-bottom
Tibia, torsion of
Toes, long
Toes, overlapping
Toes, webbing

Hand/Finger

Clinodactyly of fifth finger
Fingers, long
Metatarsus varus or adductus
Polydactyly, postaxial
Simian crease

Head/Neck

Dolichocephaly
Ear, malformations of external ear
Ear, preauricular sinus, cyst, or pit of
Fontanelle, large or small
Occiput, flat or prominent
Scaphocephaly, no mention of craniosynostosis
Neck, webbing or redundant skin folds of
Neck, short

Skin

Albinism
Birthmark, NOS
Dimple, sacral, pilonidal
Lanugo, persistent or excessive
Mongolian spots
Neonatal acne
Neoplasm, benign
Nevus, flammaeus
Skin tags on hands or feet

Urogenital Rectal

Anal fissure
Anus, skin tags of
Clitoromegaly, enlarged clitoris, hypertrophy
Hydrocele
Hymen, imperforate
Phimosis
Redundant foreskin
Scrotum, hypoplastic due to cryptorchidism
Testes, torsion of, or torsion of spermatic cord
Testes, retractile
Testicle, undescended (unilateral, bilateral or NOS)
Vagina, embryonal cyst of
Vagina, tag of

3.2. Listed Alphabetically

Albinism
Anal fissure
Anus, skin tags of
Birthmark, NOS
Breast hypertrophy
Brushfield Spots
Clinodactyly of fifth finger
Clitoromegaly, enlarged clitoris, hypertrophy
Diastasis recti
Dimple, sacral, pilonidal
Dolichocephaly
Duct, lacrimal, stenosis, stricture, or obstruction of
Ear, malformations of external ear
Ear, preauricular sinus, cyst, or pit of
Epicanthal folds
Epstein's Pearls
Esotropia
Exotropia
Fingers, long
Fontanelle, large or small
Foot, rocker-bottom
Gum cysts - includes epulis, ranula, mucocele
Hernia, inguinal or umbilical without mention of obstruction or gangrene
Hip click, with no follow-up or therapy
Hydrocele
Hymen, imperforate
Inverted nipples
Lanugo, persistent or excessive
Macrocheilia (large lips)
Metatarsus varus or adductus
Microcheilia (small lips)
Mongolian spots
Neck, short
Neck, webbing or redundant skin folds of
Neonatal acne
Neoplasm, benign
Nevus, flammaeus
Nipples, anomalies of
Nose, congenital deviation of septum of
Nose, flat bridge of
Nystagmus
Occiput, flat or prominent
Palate, high-arched
Palsy, facial
Phimosis
Polydactyly, postaxial
Protruding tongue
Redundant foreskin
Rib, cervical
Scaphocephaly, no mention of craniosynostosis
Sclera, blue
Scrotum, hypoplastic due to cryptorchidism
Simian crease
Skin tags on hands or feet
Teeth, natal
Testes, retractile
Testes, torsion of, or torsion of spermatic cord
Testicle, undescended (unilateral, bilateral or NOS)
Tibia, torsion of
Toes, long
Toes, overlapping
Toes, webbing
Tongue tie
Umbilical artery, single
Umbilical cord atrophy
Urachus, patent
Vagina, embryonal cyst of
Vagina, tag of

Appendix 4: 15 January 2020 Amendment (stamped by the Ethics Committee)

Letter of Amendment# 2 dated 15 January 2020 for the study:

A maternal short course of tenofovir disoproxil fumarate and infant vaccine to prevent mother-to-child transmission of hepatitis B virus (iTAP-2 Study)

Protocol version 1.1, dated 27 February 2019, approved by the Committee on 26 March 2019

(NIH Grant R01 HD092527, ClinicalTrials.gov NCT03343431)

Dear President of the Ethics Committee,

The Ethics Committee of Research in Humans. Institute for the Development of Human Research Protection (IHRP), Health Systems Research Institute (HSRI).

Below we propose a modification to the protocol referenced above. We would like to ask the Ethics Committee's approval to open an additional site: Vientiane Provincial Hospital, in Vientiane, Laos. We will modify the protocol (version 1.2) accordingly.

Please find below the list of sites where the study has been or will be implemented (in Protocol page 16, Table 1), with the name of the new site underlined. Please note that the name of those sites where the study has not been implemented has been crossed out.

Table 1: List of 21 study sites and planned number of participants at each site

Thailand sites	Province	Estimated number of patients to be enrolled
Health Promotion Center Region 1	Chiang Mai	15
Lamphun Hospital	Lamphun	5
Chiangrai Prachanukroh Hospital	Chiang Rai	30
Chiang Kham Hospital	Phayao	30
Prapokklao Hospital	Chantaburi	5
Banglamung Hospital	Chonburi	5
Chonburi Hospital	Chonburi	6
Nakornping Hospital	Chiang Mai	2
Nopparat Rajathanee Hospital	Bangkok	6
Samutsakhon Hospital	Samutsakhon	20
~~Kalasin Hospital~~	~~Kalasin~~	~~15~~
Samutprakarn Hospital	Samutprakarn	20
Lampang Hospital	Lampang	20

อนุมัติ
29 ม.ค. 2563
คณะกรรมการจริยธรรมการวิจัยในมนุษย์ฯ
สถาบันพัฒนาการสุขภาพแห่งชาติ (องค์การมหาชน)

~~Songkhla Hospital~~	~~Songkhla~~	~~3~~
~~Maharaj Nakhon Si Thammarat Hospital~~	~~Nakhon Si Thammarat~~	~~5~~
Lao PDR sites		
Mother and Newborn Hospital	Vientiane Capital	70
Setthathirath Hospital	Vientiane Capital	45
Mahosot Hospital	Vientiane Capital	65
Champasak Provincial Hospital	Champasak	40
Savannakhet Hospital	Savannakhet	30
~~Bolikhamxay Provincial Hospital~~	~~Bolikhamxay~~	~~15~~
Luang Prabang Provincial Hospital	Luang Prabang	15
Sayaboury Hospital	Sayaboury	20
103 Hospital	Vientiane Capital	35
Vientiane Provincial Hospital	Vientiane Capital	15
Total		~~499~~

We would like to thank the Ethics Committee for its review.

Dr. Suchada Jiamsiri

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2 9 มี.ค. 2563
คณะกรรมการจริยธรรมการวิจัยในมนุษย์ฯ
สถาบันพัฒนาการคุ้มครองการวิจัยในมนุษย์ (องค์การมหาชน)

Appendix 5: 2 December 2020 Amendment (approved by the Ethics Committee)

Letter of Amendment# 4 (2 December 2020) for the study:

A maternal short course of tenofovir disoproxil fumarate and infant vaccine to prevent mother-to-child transmission of hepatitis B virus (iTAP-2 Study)

Protocol version 1.1, dated 27 February 2019

(NIH Grant R01 HD092527, ClinicalTrials.gov NCT03343431)

Dear President of the Ethics Committee,

The Ethics Committee of Research in Humans, Institute for the Development of Human Research Protection (IHRP), Health Systems Research Institute (HSRI)

The Data Safety Monitoring Board (DSMB) for the iTAP-2 study met by teleconference on 1st April 2020 to review the evolving situation with Covid-19 pandemic and the impact of this pandemic on iTAP-2 study (please see the DSMB meeting report attached, submitted to IHRP on 28 April 2020). One of their recommendations was "any known occurrence of COVID-19 will be reported as an SAE and all participants' blood samples may be tested for SARS-CoV-2 antibodies retrospectively".

Currently no COVID-19 case has been reported among the iTAP-2 participants. To assess whether iTAP-2 participants have been exposed to SARS-CoV-2 during the pandemic period, we will test retrospectively, as recommended by the DSMB, all enrolled women for SARS-CoV-2 antibodies in blood samples collected at 2 times point, at baseline and at 2 months postpartum visit (MPP-2)

The following sentence will be incorporated into the next version (1.2) of the protocol if approved by the Ethics Committee:

All women enrolled in the study will be retrospectively assessed for SARS-CoV-2 antibodies at two time points; at entry in the study and at 2 months postpartum or before 2 months partum if no sample has been collected at 2 months postpartum.

We would like to thank the Ethics Committee for your review.

Dr. Suchada Jiamsiri

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18 ส.ค. 2564
คณะกรรมการจริยธรรมการวิจัยในมนุษย์ฯ
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