Informed consent document

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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

ClinicalTrials.gov identifier:
NCT03343431

ID/Acronym:
iTAP-2

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Participant Information Sheet

For participation in the study

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

What is the purpose of the study?

You, as well as your baby, are being invited to participate in a research study because you are pregnant and infected with hepatitis B virus (HBV). There is a small risk that this virus is passed from you to your baby during pregnancy, during delivery or after. To protect babies from HBV infection after birth, the baby should receive vaccine as soon as possible after birth so antibodies are produced by the baby and protect against the infection.

Two other methods can help prevent transmission of HBV to your baby before your baby is protected by the vaccine:7

- to administer to the baby antibodies against HBV ("HBIg"),
- to reduce the quantity of viruses in your body using an anti-HBV drug.

The purpose of this study is to determine whether taking an anti-HBV drug, tenofovir disoproxil fumarate (TDF) during the last trimester of pregnancy until two months after delivery can prevent transmission to babies as efficiently as HBIg administered to the baby at birth.

This is a consent form. It provides information about the study. Before you decide to be a part of this study, we want you to know what the study is about and what it would require from you if you decide to participate. You are free to ask questions about the study at any time. Your participation in this research study is voluntary. Refusal to participate will not involve any loss of benefits to which you are otherwise entitled. If you agree to participate in this study, the study team will ask you to sign this form and you will get one copy of this form. You may discontinue your participation at any time.

What is the nature of the Study?

Hepatitis B virus infects the liver. This virus can cause liver damage and liver cancer in adulthood. It is possible to know if people have a chronic hepatitis B infection because they have small parts of the virus called hepatitis B **surface** antigens (HBsAg) in their blood. These HBsAg can be detected by a simple blood test.

Most people with high levels of viruses in the blood have also another part of the virus called HB **e** antigen (HBeAg). HBV infected pregnant women with high levels of viruses can transmit HBV to their babies. Only pregnant women with HBsAg and HBeAg detected in the blood will be proposed to join the study. The laboratory has found these two markers in your blood.

In Thailand, the Ministry of Public Health recommends that your baby receives HB vaccine soon after birth, then at 1, 2, 4 and 6 months of age. This protects against infection early in life and for at least 20 years, probably longer. The vaccine is widely available and offered for free by the government.

Another method has been used to further reduce the risk of transmission. This method is to isolate antibodies from the blood of adults who were vaccinated, then administer these antibodies to the baby at birth, in addition to the vaccine. The preparation of HBIg is complex and costly. It is not always available in all hospitals.

However, even when using vaccine and HBIg, some infants are infected. One reason may be that vaccine and HBIg are administered at birth, thus too late if the baby has already been infected during pregnancy.

This is why, more recently, anti-HBV drugs that reduce the number of viruses in the blood and the liver have been used to prevent transmission to babies. Tenofovir disoproxil fumarate (TDF) is one of these drugs. It is approved by the Thai Food and Drug Administration for the treatment of HBV infection.

There were two recent studies, one in China and one in Thailand, in pregnant women with HBsAg and HBeAg. All infants received vaccine and HBIg, and they were tested for HBV at 6 months. In each study, about half the women received TDF and half did not receive TDF. When mothers received TDF, the quantity of viruses significantly decreased before delivery, and no babies were infected with HBV. If mothers did not receive TDF,

the quantity of virus did not change and some babies were infected (7% in China and 2% in Thailand). More than 3,000 pregnant women have received tenofovir and there is no evidence that tenofovir causes harm to the fetus. The previous two studies (in China and in Thailand) have found that tenofovir was safe.

The study will evaluate whether the risk of infection when mothers take tenofovir is lower than 2%. In this study, all mothers will receive tenofovir and all infants will receive HB vaccine. In Thailand, the Ministry of Public Health is planning for recommending this approach and HBIg will be used only if available.

If you want that your baby receives HBIg at birth, you should not participate in this study. Your doctor will explain you how you can obtain HBIg.

Who will participate?

499 HBV-infected pregnant women, at least 18 years old, will be enrolled over 2 years in Thailand and Laos.

In Thailand, it is planned to open sites in 12 hospitals: Health Promotion Center Region 1 in Chiang Mai, Lamphun Hospital, Chiang Rai Prachanukroh Hospital, Chiang Kham Hospital, Prapokklao Hospital, Banglamung Hospital, Chonburi Hospital, Nakornping Hospital in Chiang Mai, Nopparat Rajathanee Hospital in Bangkok, Samutsakorn Hospital, Samutprakarn Hospital and Lampang Hospital.

What will happen if I decide to take part in this study?

If you agree to participate in the study, we will need to determine whether you qualify for the study.

We will first propose to draw your blood (16 mL. or about 3 teaspoons) to measure creatinine, to check that your kidneys are working properly and that you can take TDF. This test must be done before starting treatment at 28 weeks of gestation.

Your physician will give you the results of the test and, according to these results, explain whether you can continue to participate in the study.

If you agree to participate, we will offer you to refer your relatives who will be in contact with the baby for a HBV test and counseling. There will be no obligation but we believe that, if they are also infected with HBV, they should take some precautions to avoid transmission to the baby early during the first weeks of life.

<u>During the study:</u>

At 28 weeks of pregnancy, your medical history will be reviewed and you will undergo a physical examination and blood draw (16 mL or about three teaspoons) for additional tests to confirm if you qualify for the study. The results of all the tests will be explained to you.

If you qualify, you will receive one bottle of study drug and the study team will explain how to take it.

After enrollment, there will be 2 study visits before you deliver: at 32 and at 36 weeks' gestation. You will receive routine medical check-ups provided at the antenatal clinic as for any pregnant woman. In addition, you will undergo a blood draw (10 mL or about two teaspoons) to assess your kidney function (creatinine) at 32 weeks, and to measure the quantity of viruses after the beginning of treatment and at the latest at 36 weeks.

When you go into labor, you should immediately go to the maternity unit. A blood draw (11 mL. or about two and a quarter teaspoons) will be performed to evaluate your liver (SGPT, SGOT) and your renal function (creatinine), and to evaluate the effect of treatment (HBV DNA viral load) and measure tenofovir plasma level.

After delivery, you will be asked to come for study visits at 1, 2, 4, 6, and 12 months to follow the effects of the treatment. You will have a physical exam and a blood draw (about 4 to 13 mL. or about one to less than three teaspoons) to monitor SGPT, SGOT and creatinine, HBeAg, and complete blood count.

<u>HBV treatment</u>

You will receive TDF 300 mg once a day to take at the same time every day, from 28 weeks gestation until two months postpartum. At each visit, the study team will ask you whether you have taken your treatment every day. It is very important to take this treatment every day to decrease the risk of transmission. However, we understand that you may miss some doses and it is important that you inform the team.

During or after the period of treatment, you should call immediately your doctor or the nurse in charge of the study (see contact numbers at the end of this form) if you suffer from another condition, in particular if you get the following signs or symptoms of liver problems:

- Your skin or the white part of your eyes turns yellow (jaundice).
- Your urine turns dark.
- Your stools turn light in color.
- You don't feel like eating food for several days or longer.
- You feel sick to your stomach (nausea).
- You have lower stomach area (abdominal) pain.

If your level of SGPT is above 60 IU/L before you start treatment, we will introduce you to a specialist who will assess your possible need for long term treatment.

Study Procedures for Your Baby.

Your baby will receive HBV vaccine within 12 hours of birth and at 1, 2, 4 and 6 months of age. You will be asked to bring your baby 1, 2, 4, 6, 9, 12, and 18 months after birth for clinical safety evaluation and determination of HBV status.

Your baby will not receive HB immune globulin at birth.

The quantity of viruses in your blood will be measured after the beginning of treatment and at the latest at 36 weeks. If it remains high, your doctor may recommend to administer HBIg to your baby at birth if it possible. In that case, the study will reimburse the HBIg.

Each visit will include a physical examination of the baby and counseling for you.

Blood sample from your baby (5 mL or about a teaspoon) will be taken at birth, 1, 2, 4, 6, 9, 12, and 18 months after birth to look for evidence of HBV infection and to check for immunization status.

Table 1: Planned blood draws

1. Mother

Visit	During pregnancy			Delivery	After delivery				Total
	28 weeks	32 weeks	36 weeks		1 months	2 months	4 months	12 months	
Blood draws (mL.)	16	10	6	11	4	13	10	8	78
Blood draws (teaspoon)	3 and 1/4	2	1 and 1/4	2 and 1/4	1	2 and 2/3	2	1 and 2/3	16

2. Infant

Visit	Birth	1 months	2 months	4 months	6 months	9 months	12 months	18 months	Total
Blood draws (mL.)	4	5	5	5	5	5	5	5	39
Blood draws (teaspoon)	1	1	1	1	1	1	1	1	8

Breastfeeding
You can breastfeed your baby. The risk to transmit HBV to your baby is not increased by breastfeeding.

Safeguards for Your Health

You and your baby will undergo careful check-ups throughout the study. It is very important that you keep all study appointments and take TDF as instructed. At each visit, you will be asked if you or your baby have suffered from any other condition, are taking any other medicines or have experienced any adverse events. If you need to, you may contact us or come to the clinic at any time, even if no visit is planned.

What is the cost for my participation?

There is no cost to you or your baby for the medication, extra clinic visits or laboratory tests associated with this study.

All study participants will receive 300 baht (in all sites except Bangkok sites where the amount will be 400 Baht) at each visit to compensate for transportation costs (if justified, the research team at site will compensate for higher transportation costs).

Significant new findings

Any significant new findings that develop during the study that could affect you, your baby, or your willingness to continue participation will be made available to you as soon as possible.

Can the research or my participation be terminated early?

Your physician could recommend that you withdraw from the study if any condition or severe adverse event developed that would make continued participation harmful to you or your baby. In such a case, you would be treated with the standard of care available. However, you should not interrupt your treatment without medical advice to avoid a sudden increase of the HBV virus in your liver without medical supervision.

What are my alternatives if I do not participate in this study?

Your alternative to participation in this study is the usual care available to a pregnant woman with HBV infection at your health care facility.

Will my medical information be kept private?

You and your baby's participation in this study will be kept confidential and will not be communicated to anyone without your written permission.

Efforts will be made to keep you and your child's personal information confidential. Your medical records will be kept confidential. They will be disclosed to you, to those heath care providers directly involved in your care and, for study monitoring or auditing purposes, to the members of the research team, the Thai Food and Drug Administration (FDA), the Ethics committee of Institute for the Development of Human Research Protections, local Ethics Committee in your hospital, study staff, study monitors, drug companies supporting this study (drug company names) and study sponsors. All study forms will be coded by number and your name will not be recorded on these forms. Only these code numbers will be kept in the study database that will be used for analysis. Any publication of this study will not use your child's name or identify you child personally. However, we cannot guarantee absolute confidentiality and your personal information may be disclosed if required by law.

What will happen to my and my baby's collected information?

All information that could contribute to your identification, such as your date and place of birth, will be kept confidentially, or destroyed at any time on your request.

What will happen to my and my baby's blood specimens?

Your blood specimens, identified by code, will be stored centrally at the special laboratory, Faculty of Associated Medical Sciences, Chiang Mai University where only approved researchers and staff will have access to them. People who work at the facility will also have access to your samples to keep track of them, but these people won't be able to identify you. The stored samples will not be used for any commercial activities.

You can withdraw your blood samples from the sample repository at any time, and they will be immediately destroyed by autoclave following the standard procedure at the Faculty of Associated Medical Sciences, Chiang Mai University.

If there is an important scientific reason to conduct studies to better understand, for example, the relationship between a person's genetic makeup (your DNA and RNA) and the risk to become infected, we may use your samples for these studies after the approval of the Ethics Committee. You may approve or refuse the storage of your blood samples and the use of your DNA for further studies by ticking the appropriate box in the consent form.

Your stored blood specimens may be also used for other evaluations that may help understand the mechanism of HBV perinatal transmission and liver damage, after the approval of the additional studies by the Ethics Committee. You are free not to agree and this will not affect your participation in the study. If you agree, please tick the appropriate boxes in the consent form.

What if I am injured during this study?

Immediate necessary care is available free of charge to you and your baby if you or your baby have a medical problem 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.

What are the potential risks and side effects for me for being in this study?

You may experience some adverse effects of the treatment used in this study, including kidney damage or failure, bone thinning, gas, dizziness, feeling tired, low phosphate in the blood and allergic reaction, which may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath or general feeling of illness.

Some people who have taken medicines like TDF have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis).

One of the main possible risks of taking tenofovir is a reactivation of the hepatitis (inflammation or irritation of the liver). You should be aware that your liver function tests may increase, and symptoms associated with hepatitis may worsen at some point during the study treatment or in the weeks or months after you stop tenofovir. This is the reason why we will ask you to come regularly at all study visits and inform your physician if you cannot come so another appointment can be scheduled.

The risks and discomforts of blood draw include pain, swelling, bruising, inflammation of a vein and fainting. If necessary, you will receive appropriate care from your physician.

What are the potential risks and side effects for my baby for being in this study?

There is a low risk that your child could be infected in the study if he receives vaccine and if you take the study treatment.

One of the potential risks associated with tenofovir during pregnancy is bone thinning in the newborn and slightly slower growth of infants but this has not been seen in the recent Thailand study.

The risks and discomforts of blood draw include pain, swelling, bruising, inflammation of a vein and fainting. If necessary, your infant will receive appropriate care from your physician.

What are the benefits for me and my baby for being in this study?

During the study, you and your baby will be provided with close medical follow-up.

Taking tenofovir may prevent the risk of transmission during pregnancy and around delivery by decreasing the amount of virus in your blood.

Providing tenofovir significantly decreased the quantity of virus in the mother at delivery and in early postpartum period which may have helped decrease transmission of HBV.

Who should I call if I have questions?

At any time, if you have further questions about this study or your rights and benefits as a participant, you may contact:

1) The investigator responsible for safeguarding your welfare and the welfare of your baby,

   Dr. _____ (co-investigator name at each site)
   Address: _____
   Telephone # Office:_____Home: _____Mobile: _____
   Fax: #_____
   or _____(name and title of Hospital Director)

2) Or your hospital's Ethics Committee

   _____ Telephone # _____,
   (Representative of your hospital's Ethics Committee)

3) **The Ethic committee of research in Humans**
   Institute for the Development of Human Research Protections,
   Health Systems Research Institute.
   Building 8, Floor 7, room 702 Medical sciences department.
   Ministry of Public Health, Nonthaburi, 11000
   Telephone: 02-5913541, 02 -5913876 – Fax: 02-5914125

Schedule of visits and Study 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 HBsAg, HBeAg, HIV and HCV serology and Ultra sound (after consent)		X								
ALT (SGPT) & AST (SGOT)		X			X		X	X		
Complete Blood Count		X			X			X		
Serum creatinine		X	X				X			
Dipstick glycosuria and proteinuria		X					X			
HBeAg										X
HBV DNA load		X		X	X					
Tenofovir plasma level (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

Schedule of visits and Study 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	X	X	X	X	X	X	X
HBV DNA PCR	X	X	X	X	X	X	X	X
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	4	5	5	5	5	5	5	5

Informed consent Form

For participation in the study

Study title: A maternal short course of tenofovir disoproxil fumarate and infant vaccine to prevent mother-to-child transmission of hepatitis B virus. Version 1.1 dated 27 February 2019

Date of consent: _____Month_____ Year_____

By signing below I confirm the following:

- The investigator/counselor has fully explained the purpose of this study, the procedures to be followed and the risks and benefits of participation and I understand them.
- The investigator/counselor has agreed to honestly answer all of my questions until I am satisfied.
- I have had sufficient time to consider participation in the study.
- I have the right to withdraw from the study at any time and my withdrawal would not affect any other care to which I am entitled. My participation in the study is completely voluntary.
- I authorize that the results of laboratory tests performed as part of my routine clinical care are recorded for this study.
- I understand that the monitor(s), the auditor(s), the *institutional review board*, and the regulatory authority (ies) will be granted direct access to my original medical records for verification of clinical trial procedures and/or data, without violating my confidentiality, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, I am authorizing such access.
- A copy of the signed information/informed consent form will be provided to me.

Name of the Investigator (available 24 hours/day):

Dr. _____ [investigator name at each site]

Address: _____

Telephone # Office: _____ Home: _____

Mobile: _____ Fax: #_____

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree for your participation and your child's participation in this study, please sign your name below.

_____	_____	_____
Participant's Name (Typed or print)	Signature	Date
_____	_____	_____
Woman's legal representative /Guardian (if appropriate)	Signature	Date
_____	_____	_____
Name of the Father of the child (If available and with the woman's consent, typed or printed)	Signature	Date
_____	_____	_____
Investigator/Counselor's Name (Typed or print)	Signature	Date

Witness' Name (Typed or print)	Signature	Date
Witness' Name (Typed or print)	Signature	Date

Informed consent form for specimen storage

Study title: A maternal short course of tenofovir disoproxil fumarate and infant vaccine to prevent mother-to-child transmission of hepatitis B virus. Version 1.1 dated 27 February 2019

Date of consent: _____Month_____ Year_____

By signing this form, I confirm the following:

- The investigator/counselor has fully explained the purpose of my and my baby's stored samples and I understand the information.
- The investigator/counselor has agreed to honestly answer all of my questions until I am satisfied.
- I am free not to give my permission for the storage of my and my baby's samples and this will not affect my participation in the study.
- I can withdraw my and my baby's blood samples from the sample repository at any time, and they will be immediately destroyed by autoclave following the standard procedure at the Faculty of Associated Medical Sciences, Chiang Mai University.

Consent for blood storage:

I give my permission for the storage and use of my and my baby's specimens for the study test(s) as discussed in the information sheet.

□Yes □No

I give my permission for the storage and use of my and my baby's specimens for future test(s):

□Yes □No

I give my permission for the storage and tests of DNA:

□Yes □No

SIGNATURE PAGE

_____	_____	_____
Participant's Name (Typed or print)	Signature	Date
_____	_____	_____
Investigator/Counselor's Name (Typed or print)	Signature	Date
_____	_____	_____
Witness' Name (Typed or print)	Signature	Date
_____	_____	_____
Witness' Name (Typed or print)	Signature	Date