UNIVERSITY OF WASHINGTON (UW) and UNIVERSITY of NAIROBI (UoN) Collaborative Study Group

CONSENT and PARENTAL PERMISSION FORM FOR RANDOMIZED TRIAL

Preventing *Mycobacterium tuberculosis* Infection in HIV-Exposed Infants

Short Title: Infant TB Infection Prevention Study ("iTIPS")

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1. **Researcher's Statement**:

We are asking you and your child to be in a research study. The purpose of this form is to give you the information you will need to help you decide whether you and your child will be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called "informed consent." This form serves as a both as a record of your consent to be in the study and as a parental permission form. We will give you a copy of this form for your records.

The word "you" in this form refers to you and your child.

2. **What you should know about this study:**

- This form explains what would happen if you join this research study.
- Please read it carefully. Take as much time as you need.
- Please ask the research team questions about anything that is not clear.
- You can ask questions about the study at any time.
- If you choose not to be in this study, it will not affect any other care received at clinic.
- If you say 'Yes' now, you can still change your mind later.
- You can quit the study at any time.
- You would not lose benefits or be penalized if you decide not to take part in the study or to quit the study later.

3. **What is the goal of this study?**

The goal of any research study is to answer questions. We (the research team listed on the front of this form and our staff) are doing this research study to answer the following question:

- Does the medicine isoniazid (INH) decrease the risk of *Mycobacterium tuberculosis* (MTB) infection?

MTB causes the disease called tuberculosis (TB). Once infected with MTB, some people go on to get TB disease. Young children, as well as people with HIV are more likely to get TB disease because their body defenses are sometimes weak. Children, even if they are not infected with HIV, are more likely to become infected with TB if someone else in their household is also infected with both HIV and TB. INH has been successfully used to

decrease the chances of getting TB disease after MTB infection, but little is known whether it can prevent getting MTB infection in the first place.

4. **Why do I have the option of joining this study?**

You have the option to take part in this research study by being an HIV-infected mother and having a baby that was exposed to HIV.

5. **How many people will take part in this study?**

We think that about 300 mothers and their infants will take place in this research study at sites in western Kenya.

6. **If I agree to join this study, what would I need to do?**

STUDY PROCEDURES

This is what will happen if you agree to participate in this study. We will ask you to read, discuss, and sign or make your mark on this form. After this form is signed or marked, the study staff will ask you questions about you and your child's health, including HIV status, questions about your pregnancy, medications, and if you have been exposed to someone with TB. A study clinician will collect up to 5 mls of blood (teaspoon) from your infant on enrollment at 6 (+4) weeks of age, 10 weeks (+/- 4) weeks of age and 12 months after starting the study, and if your infant is diagnosed with TB disease during the study. We will also ask for a stool sample from your infant. You will also be asked to give 30 mls of breast milk and 5 mls of blood at the beginning of the study. These samples will be used to study the body's defenses against TB.

You will be placed into 1 of 2 groups. You cannot choose which group you will be placed in. You will be placed in a group by chance based on a number that has been assigned to you. The two groups you may be assigned to include either 1) INH or 2) no INH. Your child's chance of getting INH or no INH is the same, just like flipping a coin.

INH group - If your infant is assigned to the INH group, you will be asked to give your child INH daily for 1 year. Although INH is well tolerated in infants, it can be associated in very rare cases with tingling, burning, or numbness in the hands and feet. To prevent this, you will also be asked to give you child a vitamin called pyroxidine. At the beginning of the study, you will be asked how you would like to receive your child's medication every month. You can choose to come to the clinic to pick it up or have a field worker bring it to your home. Also, if your child is in the INH group we will draw blood to measure your infant's baseline liver function at enrollment (before staring INH) and after taking the medicine for 4-6 weeks. The liver is the main part of the body that filters this medication in the body.

No INH group – If your infant is assigned to the no INH group, you will still have the same study procedures performed as the INH group, such as exams and blood draws, except your child will not be given INH or pyroxidine.

These tests and exams help us find out if being in this study causes any effects that are important to know about. We use them to check on the safety of the people in this study. We also use them to learn if the experimental treatment is helping or not.

You will be asked to bring your infant to clinic to be evaluated on enrollment at approximately **6 weeks of age (enrollment), 10 weeks, 14 weeks, 6 months, 9 months, and 12 months of age**. These visits are aligned with the Kenyan recommended schedule of pediatric well child/immunization visits. Additionally, you will be asked to come to the last study visit at **12 months post-enrollment**. It is very important to come to the last visit as this is the visit when we will draw blood to see if your infant has been infected with tuberculosis. If your infant is in the INH group, you will be given enough INH and pyroxidine at each visit to last until the next visit.

Tuberculin skin test (TST). A study clinician will a small needle to put some testing material, called tuberculin, just under the skin of your infant at the end of study visit and if your infant is diagnosed with TB. We will ask you to return to the clinic in 2-3 days to check the result by measuring if there is a reaction on your skin. TST is a test that is used to diagnose MTB infection, but does not necessarily mean you have TB disease.

These tests and exams help us find out if being in this study causes any effects that are important to know about. We use them to check on the safety of the people in this study. We also use them to learn if the experimental treatment is helping or not.

Blood for genetic testing – Some of the blood drawn at the beginning of the study from your infant will be stored to do a test to check the genes (NAT2) that are related to how the body filters INH. The samples that will be tested will be chosen after the study is completed. You will not be told of the result for this test because it is for investigation only and will be done after the study is completed.

Urine and hair for INH testing – For children in the INH group, we will collect urine at the 10 weeks, 14 weeks, 6 months, 9 months, 12 months of age, and study endpoint visit (approximately 14 months of age). This urine will be used to test for INH in the clinic using a dipstick. We will also cut a small thatch of hair (approximately 30 strands) at the end of study visit. This hair will be used to measure INH. You will not be told of the result for this test on hair because it is for investigation only and will be done after the study is completed.

MEDICAL RECORD INFORMATION

We will ask for access to your and your baby's clinic and pharmacy records to find out more information about your pregnancy, delivery, and postpartum care. If you agree to give us access to your medical records, we will get information from the clinics where you received care before, during, and after delivery of your baby, including: any health problems, medication adherence and side effects, and your baby's health information. We will also record laboratory test results, like your CD4 and HIV viral load tests, and infant's HIV tests.

7. **How long would I be in this study?**

If you choose to take part in all the study visits, you and your infant would be in the study for 1 year. If you join this study, you can decide to stop **at any time, for any reason**. If you decide to stop you would need to talk with site investigators so you leave the study in a safe way.

The research study clinicians could also decide to take you out of this study. This might happen if we find out that it is not safe for you to continue in the study. It may also happen if you cannot come to enough of the study visits. If we ask you to leave the study we would always explain why and this would not hamper other care received at the facility in any way.

8. **What are the potential harms or risks if I join this study?**

There are potential harms or risks if you take part in this study. Some are common and some are rare. They are described below.

Potential Harms and Discomforts (from the most common, to the most rare):

- Local irritation due to blood draw
- Local irritation due to TST
- Maternal breast discomfort due to self-expression of breast milk
- Nausea, vomiting, stomach discomfort due to INH
- Peripheral neuropathy (numbness, tingling of the nerves in your hands and feet) due to INH
- Hepatitis (irritation of the liver which is the organ that filters the medicine INH)
- Some people feel uncomfortable answering questions about their health and their baby's health

Because this research study involves a medication that has been used primarily to treat TB disease or prevent TB disease in the past (not prevent MTB infection): we do know that in general INH is generally well tolerated by infants.

A Data Safety Monitoring Board (DSMB) will review the information from this research study. This board is made up of a group of experts responsible for looking at how people in the research study are doing. If you take part, we would tell you about any new information we learn that might affect your health or your willingness to stay in the study.

9. **What are the potential benefits if I join this study?**

Potential Benefits for You:

Being in this study might benefit you in the following ways:

- Participants will benefit from direct medical care in the long-term research group.

Potential Benefits for Others:

- All infants - those born to HIV infected mothers and those born to uninfected mothers - will benefit from a better understanding in how the body defenses protect against MTB infection
- We hope to use information we gain in this study to benefit others in regions with high tuberculosis rates.

10. **What other options do I have?**

Whether or not you decide to participate in this research study, you can continue to receive your mother-child health care at this clinic.

11. **Who is funding this study?**

The study team and/or the University of Washington and Kenyatta National Hospital are receiving financial support from the Thrasher Research Foundation Health in the United States.

12. **How would you keep my information confidential?**

We will keep your identity as a research subject confidential. Your HIV test results, your infants MTB infection test results, medical records, and responses to questions will be kept private, and no identifying information of any kind will be released to any other person or agency that is not working on this study, without your permission in writing. We will not publish or discuss in public anything that could identify you. Any specimens you provide, and your medical information will be identified by a code number. All of your information, including the link between your name and code number will be kept in a secure location at the clinic only. Once the study is completed, we will maintain the link for 5 years, after this time we will remove your name and all identifying information from the study files. Any publication of this study will not use your name or identify you personally. However, study team may share identifiable information about you in the case the study team becomes aware of possible harm to yourself or others.

Although we will make every effort to keep your information confidential, no system for protecting your confidentiality can be completely secure. It is still possible that someone could find out you were in this study and could find out information about you. Government or university staff may review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

Study records may be reviewed by:

- University of Washington, including the Institutional Review Board
- Kenyatta National Hospital and University of Nairobi, including the Ethics and Research
- Committee
- Kenya Medical Research Institute (KEMRI)

A description of this clinical trial will be available on http://www.clinical.trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. A copy of your consent form will be placed in your study record.

13. **Would it cost me money to be in this study?**

If you take part in this study there would be no cost to you.

14. **What if I were injured because I joined this study?**

If you think you or your infant has a medical problem or illness related to this research, contact Dr. John Kinuthia**:** +254-722-799-052 right away. He will treat you or refer you for treatment. If your child is injured as a result of being in the study, you will be offered free care at the study clinic. If you require medical care that the study clinic cannot provide, we will refer you to the appropriate organizations to receive care for the injury. The costs of the treatment may be billed to you or the National Hospital Insurance Fund (NHIF) just like other medical costs, or it may be covered by the UW's discretionary Human Subject's Assistance Program (HSAP) depending on a number of factors. The researcher may request HSAP coverage by following established procedures. If you wish to request HSAP coverage yourself, you may contact the researchers listed on the first page, or the UW Human Subjects Division at hsdinfo@uw.edu or +1-206-543-0098. Ask the researchers if you would like information about the limits and conditions of the HSAP. The UW does not normally provide any other form of compensation for Injury. However, the law may allow you to seek payment for injury-related expenses if they are caused by malpractice or the fault of the researchers. You do not give up any legal rights by signing this consent form.

15. **Would I be paid of I join this study?**

Participants will be provided a stipend for travel.

16. **If I join the study, can I stop?**

Yes. Taking part in research is always a choice. If you decide not to be in the study, you can change your mind at any time. We ask that you tell Daniel Matemo who can be reached at +254-722-322-378.

If you choose to leave the study, it will not affect your care at the study site. You will not lose any benefits or be penalized if you choose to leave the study. We may ask you to come for a visit if you leave the study early. At that visit we may ask to collect 5 mls of blood (teaspoon) and place a TST like we would at the end of the study visit.

17. **Will my samples be used after this study is done?**

We would like to save samples of your blood and breast milk and your baby's blood,stool, and hair at the KEMRI/CDC, University of Nairobi, the University of Washington, the Fred Hutchinson Cancer Research Center, Emory University, or the University of California, San Francisco, for future HIV and/or TB related research and maternal and infant health. This may include testing for genes which may affect whether a person is more or less likely to get infections, or things that may affect infant and maternal health (mother's health during postpartum period with special emphasis on HIV-related illnesses, infant health with special emphasis on HIV-exposure, and TB exposure).

Information we get from you, and your samples, may be shared with other investigators studying HIV, TB, or mother and child health. We will not share your name or any identifying information with them. An Institutional Review Board or Independent Ethics Committee, which looks at study application to ensure the safety and rights of research participants, must approve future research studies in which we will use your or your baby's samples to obtain information about both of you. Permission from the University of Nairobi's Ethics Committee will be sought before any of these samples are used for future research. These tests are for research and are not useful for your or your baby's clinical care. Before your samples or your baby's samples leave the clinic, they will be assigned a code and your name or your baby's name will not be on them. We will store these samples for ten years after completion of the study. Storage of samples past this time period will only occur with approval from an Institutional Review Board and Ethics Committee.

If you do not want to have your or your baby's samples saved for future research, you can still be in this study and your or your baby's samples will be destroyed once testing for the study is completed. If you agree to store your or your baby's samples now, but change your mind before the end of the study, let the study staff know and we will make sure that your or your baby's samples do not get stored for future research. We will not sell your or your baby's samples. Tests done on your or your baby's samples may lead to a new invention or discovery. We have no plans to share any money or other benefits resulting from any potential invention or discovery with you.

CONSENT FOR STUDY PARTICIPATION

Subject's statement:

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, I can ask one of the researchers listed above. If I have questions about my rights as a research subject, I can call the *Kenyatta National Hospital Ethics and Research Committee, at 2726300 Ext. 44102*. I give permission to the researchers to use my medical records including my baby's as described in this consent form. I will receive a copy of this consent form.

_____	_____	_____
Printed name of subject	Signature or thumbprint of subject	Date
_____	_____	_____
Witness Name (if caregiver illiterate)	Witness Signature	Date

CONSENT FOR SAMPLE STORAGE FOR FUTURE STUDIES INCLUDING GENETIC TESTING

Please mark, one option for each question below:

YES ___NO___ You can store **my** samples for **future research** into HIV, TB or maternal child health

YES ___NO___ You can store samples from **my baby** for **future research** into HIV, TB or maternal child health

YES ___NO___ You can store my samples for future research into HIV, TB or maternal child health **including genetic testing**

YES ___NO___ You can store samples from my baby for future research into HIV, TB or maternal child health **including genetic testing**

_____	_____	_____
Printed name of subject	Signature or thumbprint of subject	Date
_____	_____	_____
Witness Name (if caregiver illiterate)	Witness Signature	Date

Who do I contact if I have problems or questions?
If you ever have any questions about this study, or if you have a research-related injury, you should contact Dr. John Kinuthia. If you have questions about your rights as a research participant, you should contact the Kenyatta National Hospital Ethics and Research Committee, at 2726300 Ext. 44102.

_____	_____	_____
Printed name of study staff obtaining consent	Signature	Date

Copies to: Researcher, Participant