

Consent for Mpepu Research Study of Infant Survival in Botswana Main Study Consent, for HIV-Infected Mothers

1. INTRODUCTION

- You and your baby are being invited to take part in a research study. This study is sponsored by the National Institutes of Health (NIH) in the United States, and is being done together by researchers at the Harvard School of Public Health and the Government of Botswana. The investigators in charge of this study are Dr. Roger Shapiro, Dr. Shahin Lockman, and Dr. Joseph Makhema. The purpose of this study is to find ways to improve infant health and survival among infants whose mothers are HIV-infected but who do not themselves have HIV. To decide whether or not you wish to take part in this study, you should understand enough about its risks and benefits to make the best decision for you and your baby.
- This consent form gives information about the research study, which the study team will discuss with you. Once you understand the study, and if you agree to take part, we will ask you to sign this consent form and will offer you a copy to keep.
- It is important that you understand the following:
 - ✓ Your taking part in the study is completely voluntary.
 - ✓ You may refuse to take part in the study or leave it at any time without the loss of other benefits to you.
 - ✓ Your decision to leave the study will not affect your future medical care or your ability to take part in other studies.

2. WHY IS THIS STUDY BEING DONE?

- Infants born to women who are HIV-infected have a high risk of dying in the first year of life, even if the infant is not HIV-infected.
 - In a previous study in Botswana (the Mashi Study), about 7 of every 100 HIV-negative babies died before 18 months of age.
- This study will look at 2 possible ways to help more infants survive:
 - 1) A common antibiotic medicine called cotrimoxazole (CTX) has been shown to reduce the risk of death from many different causes for HIV-*infected* infants, but it is unknown whether it also protects HIV-*uninfected* infants during the first year of life. One of the reasons for doing this study is to find out if CTX protects HIV-uninfected infants.
 - 2) Another aim of this study, for women who choose to breastfeed, is to find out if a longer period of breastfeeding is best for HIV-exposed infants in Botswana. The World Health Organization recommends 12 months of breastfeeding for infants protected by antiretrovirals (ARVs) given to either mothers or to infants. The current policy in Botswana is to recommend that mothers who choose to breastfeed stop by 6 months. It is unknown whether 6 months or 12 months of breastfeeding is safest for infants in Botswana. Longer breastfeeding may save the lives of some babies, but it may also increase the chance that a baby will get HIV by a small amount. To lower the risk of a baby getting HIV, breastfeeding women in this study will either be receiving highly active antiretroviral therapy (HAART) or their infants will be receiving a drug called nevirapine (NVP). The use of these ARVs in either

mothers or infants can lower (but not entirely get rid of) the risk of HIV transmission during breastfeeding, while allowing infants to receive the benefits of breast milk.

3. OVERVIEW OF THE STUDY

The study will enroll a total of 3,724 HIV-infected women, and their HIV-uninfected infants, by 34 days of infant age. From 14 to 34 days of age, babies will start to receive either active CTX study drug or a placebo (sugar pill) through 15 months. The choice of groups will be made by a computer, and there will be an equal chance for your baby to be in either group. Neither you nor study investigators will know which group your baby is in. Your baby will be followed closely through 18 months of age.

Babies who are breastfeeding from 14-34 days of age will also be separated into 2 additional groups by a computer, with an equal chance of being in either group: half of the breastfeeding babies will breastfeed until 6 months, and the other half will breastfeed for 12 months. At each study visit, our staff will support mothers in sustaining breastfeeding for the duration to which her baby is assigned. All infants will continue to receive either CTX or placebo until 15 months, and will have complete follow-up until 18 months, no matter how long they actually breastfeed. Babies whose mothers chose to formula feed can continue to formula feed and take part in the CTX part of the study.

The primary objective of the study is to see whether more infants are alive at 18 months if they received the CTX. An important secondary objective is to see whether more breastfed infants are both alive and HIV-uninfected at 18 months if they were assigned to breastfeed for 12 months.

All women and infants in the study will receive standard-of-care ARVs from the Botswana government to prevent mother-to-child HIV transmission (MTCT), and all will choose a feeding method with counseling. The only difference will be that infants in this study will be given NVP prophylaxis in the first 4 weeks of life rather than ZDV, to reduce the chance of low blood counts that might occur with CTX and ZDV together. Breastfed infants will continue to receive NVP until weaning if a woman is not on HAART.

4. WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Enrollment

- Before joining the study, you will be asked about your medical history and your ability to be followed at the study clinics. If you have already delivered your baby, an assessment of the health of your baby will be performed as well.

Study Entry and Follow-up Before Delivery

- If you qualify and choose to take part in this study when you are at least 26 weeks pregnant, we will enroll you in the study. We will help you find out if you qualify to start HAART through the government PMTCT or ART Programmes, if this has not yet occurred. We will also ask you questions about your medical and pregnancy history. This visit will take about 1 hour.

Labour and Delivery and First 4 Weeks

- After delivery, you and your baby will be checked in the maternity ward. If you have not yet enrolled, you will be offered the chance to join the study. You and your baby will have

blood drawn at this time. Tests will be run on the blood, including a test of your blood count, a test of the virus level, and CD4 cell count (which is a test of your body's immune system). An HIV test for your baby will also be done. The total amount of blood drawn at this visit will be less than two tablespoons for you, and only a few drops for your baby. You will be given NVP syrup for your baby to take in the first month of life (or longer if you are breastfeeding and not on HAART).

Randomization Visit

- You and your baby will be asked to return to the study clinic at 14 to 28 days, and will be randomized (meaning assigned at random, by a computer) to start the intervention between 14 and 34 days, depending on the baby's weight and gestational age at birth.
- At randomization, all babies who are not known to be HIV-infected will receive either CTX or placebo syrup (starting at 2.5mL or one-half a teaspoon per day). A placebo is a sugar pill which does not have active medicine in it.
- If your baby is breastfeeding at this visit, and if you are willing to breastfeed for up to 12 months, he/she will also be randomized to either 6 months or 12 months of breastfeeding, with ongoing ARV prophylaxis to either you or your baby. We will ask you to continue breastfeeding at this time. Additional NVP will be provided to your baby if you are not taking HAART or if you have not been taking HAART for at least 6 weeks.
- At this visit, both you and your baby will have a physical examination and medical history. Your baby will have another 1 teaspoon of blood drawn to do an HIV test, a complete blood count, and blood stored for future testing. You will have blood (1 tablespoon) and, if breastfeeding, breast milk (1-2 tablespoons) stored for future testing.

Follow-up After Randomization

- You and your baby will have scheduled study visits at 2, 3, 6, 9, 12, 15, and 18 months. Laboratory testing for your baby will occur throughout the study to assess your baby's health and for side effects of study drugs. This will require taking blood from your baby. The total amount of blood drawn at each visit through 12 months will not be more than half a teaspoon (2.5 ml) for your baby and it will be less than this at most of these visits (total blood drawn from your baby at 15 and 18 months will not exceed 1 teaspoon). Some of the stored blood from you and your baby will be used to determine nutritional status (including Vitamin D levels) and markers for how well your immune systems are functioning. These tests will not be available in real time. Additional laboratory testing for you will only occur if you are receiving HAART and if they are needed to provide the best HAART-related care for you (for example, a virus level needs to be checked because of missed ARV doses).
- When possible, the results of tests done will be shared with you if you would like to know them, and your baby will be offered treatment or referral for medical conditions for which there is treatment. You will be asked questions about the health of your baby at all visits. If your baby is breastfeeding, a blood sample for HIV testing will be taken from your baby at 3, 6, 9, 12, and 15 months of age for HIV testing. At 18 months of age, as recommended by the Botswana government, all babies will also be HIV tested. A complete blood count will be checked at 3, 6 and 15 months (and possibly 18 months), and, if you agree, blood will be stored at 15 and 18 months for future testing.
- All randomized infants will be followed to 18 months. Any babies who test positive for HIV will be recalled for re-testing, and confirmed infected babies will be referred for medical care. HIV+ babies will receive CTX (and be taken off the study CTX/placebo). HIV+ babies will be referred to a government ART clinic to receive HAART

- Some of the future tests for this study may require us to study your or your baby's genes. Genes contain information which is different for each person. This is done to see if either of you is at higher risk for certain drug reactions and as a marker for your (or your child's) ability to fight the HIV virus.
- If you agree (at the end of this consent form), some of your / your baby's blood and / or body fluids taken as part of this study will be stored for up to 10 years after the end of this study, in the BHP laboratory in Gaborone for approved AIDS-related research in the future. You can still take part in this study even if you decide to not allow your/your baby's leftover samples to be stored for future approved research. No personal identifiers will ever be stored, so your / your baby's identity will be protected in the usual way (see Section 7, Confidentiality of Records). Some of these samples may be shipped outside of Botswana, but only for specialized testing that is not available in Botswana. You may ask that your samples be destroyed if you later change your mind and do not want us to keep them. You can request this at any visit, or after the study by calling Dr. Joseph Makhema (Tel: 3902671, Cell 72100846).

5. HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 3,724 women and their infants will take part in this study.

6. HOW LONG WILL I BE IN THIS STUDY?

You will be in this study between 17 and 21 months, depending on whether you first enroll in pregnancy or shortly after delivery. Your baby will be in this study until 18 months of age.

7. WHY WOULD THE STUDY INVESTIGATORS TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you/your baby off the study early without your permission if:

- the study is stopped by the Botswana Ministry of Health, National Institutes of Health (NIH), the drug companies supporting this study, or the study Institutional Review Boards (IRBs) (An IRB is a committee that watches over the safety and rights of research participants.)
- a Data Safety Monitoring Board (DSMB) recommends that the study be stopped early (A DSMB is an outside group of experts who monitors the study.)
- you are not able to attend the study visits as required by the study

The study investigators may also need to take your baby off the study drug(s) without your permission if:

- continuing the study drug(s) may be harmful to your baby
- your baby needs a treatment that he/she may not take while on the study
- your baby is not able to take the study drug(s) as required by the study

If your baby must stop taking the study drug(s) before the study is over, the study investigators may ask you/your baby to continue to be part of the study and return for some study visits and tests.

8. CAN I LEAVE THE STUDY IF I CHANGE MY MIND?

You may leave the study at any time for any reason, and you will still be given medical care. If you decide to leave the study, you may be asked for a final study visit and possibly to give a final

blood sample from your baby. You do not have to give these if you do not want to. If you leave the study, the data collected until that date will remain part of the study data base.

9. WHAT ARE THE RISKS OF THE STUDY?

The medicines your baby will receive through this study are the same medicines that are given to prevent mother-to-child HIV transmission (MTCT) throughout the world, and to prevent infections among HIV-exposed or known HIV-infected babies. There is risk of infecting your baby during longer breastfeeding, but this may or may not be less than the benefits of breastfeeding.

RISKS TO YOU

- Because you will not receive any study drugs through this study, this study has no direct risks to you. You may be receiving HAART from the Botswana government, but this will not be administered by the study staff.

RISKS TO YOUR BABY

- Your baby could possibly get HIV from breastfeeding. The ARVs you will receive either from the Botswana government, or which your baby will receive from the study, will reduce this risk but cannot entirely eliminate it. About 1 baby out of 100 will become HIV-infected by 6 months while breastfeeding, even if ARVs are used. After 6 months, the risk is unknown, but it is expected to be similar. The risk of HIV infection from breastfeeding with ARVs is probably lower than the risk of death if your baby does not breastfeed during the first 6 months of life, but this is not known for certain for babies between 6 and 12 months.
- There may be side effects from the study drugs that your baby receives, even though CTX is one of the most common drugs given to infants in Botswana. If your baby receives active CTX, he/she has a small chance of developing skin rash, yellowing of the eyes or skin, nausea (feeling sick to the stomach) and vomiting, loss of appetite, stomach pain, loose or watery stools, neutropenia (decrease in neutrophils, a type of white blood cell, which helps fight infection), anemia (decrease in the number of red blood cells, which may cause your baby to feel tired), sensitivity to light, trouble sleeping, weakness and fatigue. In general, these side effects only last a short time. In rare circumstances, premature infants receiving CTX may develop problems in their brain if given CTX in the first week of life; to avoid this we will not give CTX to any babies until 2 weeks and we will not give it to premature babies until 4 weeks. Your baby will be checked for all side effects monthly. For your baby's safety, you will need to tell the study staff about all medicines your baby is taking throughout the study.
- If your baby gets diarrhea or pneumonia while taking part in this study, CTX may not be reliable for treating these infections because it is possible that resistance will develop to it if your baby is receiving the active CTX. Your baby's study team will know this, and will make this known to all other treatment providers. Other treatment agents will be available to your baby if he/she becomes sick.
- Babies who receive NVP to prevent HIV infection may develop a rash or liver problems. When used in the lower doses to prevent HIV as in this study, rashes from NVP are not common and are usually not severe in babies. However, very rarely the rash may be severe, and in some rare cases it can lead to admission to the hospital and death. This can usually be avoided by stopping the NVP when asked to do so by the study staff. At the time you and your baby leave the hospital or clinic, you will be told what to do if you see

any rash on you or your baby. It is very important that you come to the study clinic or tell the study nurse right away about any rash or other problems.

Liver problems may also be caused by NVP in rare cases. However, this has only been seen with use of much higher doses of nevirapine than will be used in this study. It was not seen in safety studies done with uninfected babies given NVP daily for up to six months. We will monitor your baby clinically for liver problems, and with laboratory tests as needed. An infant with liver disease may seem tired or sleepy, feed poorly, have pale stool, darkened urine, yellowing of the eyes or skin, pain around the liver, or abnormal tests of the liver. An infant with an active infection in the liver (hepatitis B or C) is more likely to have their liver disease get worse.

In studies of over 2,000 babies who received one dose of NVP within 2-3 days after birth, or daily NVP until 6-14 weeks of age, no serious rashes or liver problems related to NVP were found. The doses of NVP to be given in this study are much lower than those given for treatment of HIV. In a study of babies who received nevirapine every day, once a week or twice a week for up to 6 months while breastfeeding, no serious rash, liver or kidney disease were found.

Rare reactions to NVP may include fever, muscle or joint pain, blisters, sores in the mouth, swelling of the face, red eyes and irritation of the eyes, general irritability, kidney problems and/or changes in your baby's white blood cell levels. Rarely these problems have been fatal. If your baby gets any serious side effects, no matter how long he/she has been taking NVP, you need to stop giving the NVP and bring your baby to the study clinic right away or contact the medical staff at the site. The study staff will check your baby and advise you whether to continue the study drug NVP.

- There may be risks of continuing NVP if your baby becomes infected with HIV – this may make the HIV infection become resistant to the NVP, which may mean that nevirapine and other drugs like nevirapine will not work as well to treat the baby's HIV in the future. If your baby is found to be infected with HIV during the study, you will be told to stop giving him/her the NVP. We will give you and your baby's doctor the needed information about the NVP that your baby took so the best choices can be made about your baby's future HIV treatment.
- If you decide to breastfeed and you are taking HAART, some of these medicines are likely to pass to your baby. This is part of the reason these medicines may protect your baby from HIV, but it also may be a small risk to the baby. The long-term risks of this small amount of ARV exposure are unknown. There is a small possibility of your baby having a reaction to your HAART. We will want to monitor your baby for any sign of toxicity so that we can prevent any serious toxicity to your baby. The benefit of these drugs in preventing the baby from becoming HIV positive is thought to be greater than the possible risks when taken during breastfeeding, and their use during breastfeeding is recommended in WHO guidelines.

RISKS OF TAKING BLOOD

- Taking blood may cause some discomfort, bleeding, or bruising where the needle pricks your/your baby's skin, and in rare cases, fainting/feeling lightheaded or infection. A clot may form at the site of the needle prick.

RISK OF STIGMA

We will try to protect the confidentiality of your HIV status. We will visit your home only if you have granted permission for this in writing (and you may change your mind about this at any time). In all cases, home visits will be by health workers in plain clothes and in unmarked vehicles or on foot. If your HIV status were to become known or suspected because of your participation in this study, it is possible that the stigma of HIV could affect your personal relationships or even lead to the loss of your job. This might cause you stress. We will do everything possible to prevent this from happening, and confidential counseling also will be available to you through this clinic.

All blood and breast milk samples will be coded and will not identify you or your baby personally. Although your or your child's name will not be with your blood sample, it will have other facts about you or your child, such as race, ethnicity, and sex. Such facts are important because they will help us learn if genetic risk factors for HIV/AIDS are the same or different in men and women and in people from different parts of the world. Thus, it is possible that study findings could one day help people of the same race, ethnicity, or sex as you. However, it is also possible through these kinds of studies that genetic traits might come to be associated with your group. In some cases, this could reinforce harmful stereotypes.

10. ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to your baby, but no guarantee can be made. It is also possible that your baby may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

- Those babies who receive active CTX may be protected against some early childhood infections, and this may improve their survival.
- Breastfeeding is the ideal way to feed a child in the absence of maternal HIV infection. If you do not receive HAART from the government, study-provided NVP for your baby may reduce the risk of HIV transmission through breastfeeding to a very low level. This will allow for safer breastfeeding, and it may improve your baby's chances of survival as compared to either breastfeeding without any ARV protection or compared with formula feeding.
- By taking part in this study, your child may benefit from early diagnosis and treatment of HIV infection, or from early confirmation that he/she is not infected. You and your baby will receive medical evaluations by the study team, and the study staff will help with care referrals when needed.
- Knowledge gained from this study may help other pregnant women with HIV and their babies in the future.

11. WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you may choose not to take part in the study and your baby will be cared for at a government antenatal clinic.

12. WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to keep your personal information confidential. We cannot guarantee complete confidentiality. Your personal information may be disclosed if required by law.

- Your records may be reviewed and photocopied by the Botswana and Harvard School of Public Health IRBs, the Botswana Ministry of Health, National Institutes of Health (NIH), study staff, study monitors, and drug companies supporting this study.
- You and your baby will be identified by a code number only known to you, the study team, or the health staff responsible for your care. All information about you and your baby will be identified by this number. The code will be stored in a secure location. You and your baby will not be identified by name in any publication or presentation from this study.

13. HOW WILL MY/MY BABY'S SAFETY BE PROTECTED?

- Your baby will be followed throughout the study by the study staff. If any problems are found, study medications may be stopped for a short time or permanently.
- Counseling services will be available for you if needed throughout the study.

14. WHAT ARE THE COSTS TO ME?

- There is no cost to you or your baby for the medicines, clinic visits or laboratory tests related to this study. All other medical examinations or tests and medicines outside of this study will be given to you either through the study clinic or at a government clinic or hospital.

15. WILL I RECEIVE ANY PAYMENT?

- You will receive no money for your or your baby's participation in the study, but you will be given money for transportation costs to and from the clinic and to compensate you for your time (approximately 30 pula for most visits).

16. WHAT HAPPENS IF I AM INJURED?

- Immediate, necessary care will be given to you if you or your baby becomes injured due to taking part in this study. However, no financial compensation will be given.
- If you are injured because of this study, you should contact any of the following:
 - ✓ Dr. Joseph Makhema: Tel: 3902671 Cell: 72100846
 - ✓ Dr. Gbolahan Ajibola Tel: 3902671 Cell: 72115318

17. WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. You will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, wellbeing or willingness to stay in this study. If you want the results of the study, ask the study staff.

18. WHAT IF I HAVE QUESTIONS OR PROBLEMS?

- If you have any questions about this study or your rights as a participant, either while participating or after you have completed the study, you should contact:
 - ✓ Dr. Joseph Makhema (for study-related questions): Tel: 3902671 Cell: 72100846
 - ✓ Mr. Pilate Khulumani (for rights as a participant): Tel: 3632775 Cell: 71424495

Mpepu Study Consent

Overall Study Participation

The purpose of the study, procedures to be followed, and risks and benefits have been explained to me. By signing or placing my fingerprint below, I am agreeing to participate in this study. I also give consent for BHP study staff to access and use the information in my medical records if needed for the purposes of the study. I understand that this may involve photocopying any of my medical records relevant to this study. I understand that I may withdraw my participation or my baby's participation at any time without affecting my rights or those of my baby to receive medical care. I understand that this consent form takes the place of any previous consent form I may have already signed for this study, and that it applies to any information or specimens that have already been stored as part of this study.

Participant's name (first-last): _____

Participant's Omang / Passport number:

OR Participant's Omang receipt number:

Signature or fingerprint of the participant: _____

Date of participant's signature: ____/____/____ (dd/mm/yy)

Consent for Storage and Use of Blood and Bodily Fluids Specimens

The purpose of storing and potentially using my blood samples or breast milk or blood samples from my baby has been explained to me. I understand that remaining leftover samples of my blood or bodily fluids or my baby's blood obtained in the routine course of the Mpepu study may be stored for up to 10 years after the end of this study in the BHP laboratory in Gaborone for approved HIV-related research in the future. I understand that these specimens will contain no personal identifiers. I also understand that I may ask for my or my baby's stored samples to be destroyed, if I later change my mind, by notifying an Mpepu staff member during any study visit or, if I change my mind after the end of the study, by contacting Dr. Joseph Makhema (Tel: 3902671, Cell 73100846). I understand that I can still take part in this research even if I do not agree to store my/my baby's leftover samples for future approved research. By signing below, I agree to store samples for future approved health research (note: if this is not signed, it indicates that permission was not given to store samples for this purpose).

Signature or fingerprint of the participant: _____

Date of participant's signature: ____/____/____ (dd/mm/yy)

Witness : (for use when a participant is illiterate, in addition to the participant's thumbprint; when possible, witness should not be study recruiter).

The purpose of this study and the procedures, risks and benefits to her and her baby have been explained to the participant. To the best of my knowledge she understands the purpose, procedure, risks and benefits to her and her baby.

Witness's signature _____

Witness's name (first - last) _____

Date of signature ____/____/____ (dd/mm/yy)

I have explained the purpose of the HAART and MTCT Study to the participant. To the best of my knowledge, she understands the purpose, procedures, risks and benefits to her and her baby.

Health officer's name: _____

Health officer's signature: _____

Date of signature ____/____/____ (dd/mm/yy)