IRB HSR # _____ DMID # _____
A Randomized Clinical Trial of Early Empiric Anti-Mycobacterium Tuberculosis Therapy for Sepsis in Sub-Saharan Africa (ATLAS trial)

Participant's Name_____

INTERNATIONAL RESEARCH CONSENT FORM
--CONSENT TO PARTICIPATE IN A RESEARCH STUDY--

What is this study about?

This is a research study to find which medicines work better to treat sepsis caused by tuberculosis (TB). Sepsis is a serious infection in the blood. It can cause death when the body cannot fight the infection. Many people living with HIV in Uganda and Tanzania are carrying TB germs in their bodies but do not know it. The doctors think that immediately giving TB medicine to people living with HIV who are diagnosed with sepsis could improve their chances of surviving. Doctors at the Kibong'oto Infectious Diseases Hospital, Mbarara University of Science and Technology and the University of Virginia in the United States are trying to learn more about the best ways to treat sepsis.

Our team will compare results between four groups of participants who are admitted to the Mbarara Regional Referral Hospital in Mbarara, Uganda, or Kibong'oto Infectious Diseases Hospital in Kilimanjaro or affiliated hospitals in the Kilimanjaro region of Tanzania: (1) participants who receive regular sepsis medical care and standard dose of TB medicine if they are diagnosed with TB (drugs begin immediately after a diagnosis of TB is made), (2) participants who receive regular sepsis medical care, plus immediate anti-TB medicine at the standard dose (drugs begin immediately on the day you begin the study), (3) participants who receive regular sepsis medical care, plus a higher dose of TB medicine for research if they are diagnosed with TB, and (4) participants who receive regular sepsis medical care, plus immediate anti-TB medicine at a higher dose for research . If no diagnosis of TB is made, study participants will not receive TB medicine unless they are in one of the two groups that receive immediate TB medicine.

All groups receive regular sepsis care, plus you will be assigned to 1 of the 4 groups by a computer. If you join this study, you will not be able to pick which group you are in. If you do NOT join the study, you will receive medical care like Group 1.

- Group 1: Standard-dose of TB drugs begin after a TB diagnosis is made
- Group 2: Standard-dose of TB drugs begin immediately
- Group 3: High-dose of TB drugs begin after a TB diagnosis is made
- Group 4: High-dose of TB drugs begin immediately

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The reason to do this research study is to find a better way to treat people living with HIV who are diagnosed with sepsis and to improve their chances of surviving, especially during the first week after being admitted to the hospital.

You are asked to be a participant in this research study because you are living with HIV and have been diagnosed with sepsis**.**

The researchers in charge of this study are Dr. Stellah Mpagama of Kibong'oto Infectious Disease Hospital in Kilimanjaro, Tanzania, Dr. Conrad Muzoora of Mbarara University of Science and Technology in Mbarara, Uganda, Dr. Christopher Moore of the University of Virginia (USA) and Dr. Scott Heysell of the University of Virginia (USA).

This study will take place at Mbarara Regional Referral Hospital and Kibong'oto Infectious Diseases Hospital as well as the affiliated hospitals in the Kilimanjaro region of Tanzania. If you participate in this study, you would be one of 436 participants and your involvement would last until you complete TB treatment (no longer than 6 months after study enrollment).

What will happen during the study?

If you agree to participate, we will have six in-person visits and monthly telephone follow-up calls until your TB treatment ends. Detailed information about these visits/follow-ups include:

#1 Enrollment study day 1: This will be a 2-night visit in the hospital. The minimum length of stay in the hospital will be the time required to complete research blood draws. Routine care is 2 days or longer for patients admitted with sepsis.
If you agree to participate, you will read and sign this consent form before any study procedures take place.

- You will get routine antibiotics for the treatment of sepsis.
- A computer will assign you to one of the four TB-treatment study groups:
  - Group 1: Standard-dose of TB drugs begin after a TB diagnosis is made
  - Group 2: Standard-dose of TB drugs begin immediately
  - Group 3: High-dose of TB drugs begin after a TB diagnosis is made
  - Group 4: High-dose of TB drugs begin immediately
- You will be asked some questions about current symptoms, past medical history and medications.
- We will document your vital signs, height and weight and perform a physical exam.
- You will have your blood drawn by a nurse/doctor

- This blood will be used to check your HIV status, blood counts, and test for other germs in your blood that can be making you sick. The tests will be performed at the hospital and a research laboratory nearby. Results will be given to you and your doctors.
- Any leftover blood or urine samples will be stored at the laboratory until the conclusion of the study. At the conclusion of the study, deidentified samples will be stored for their possible use in future studies. We will not perform any genetic tests on your blood samples.

- You will be asked to provide a urine sample.
  - The urine will be used to check for the *Mycobacterium tuberculosis*, the germ that causes tuberculosis (TB) and other germs that could be making you sick. (For female participants): A pregnancy test will be checked from the urine. If you are pregnant, you will not be eligible for the study.
  - Any leftover urine will be stored at the laboratory until the conclusion of the study.
- If you allow us to store your blood and urine samples, it means that you will be giving them to us for testing and for research. The samples will be under the responsibility of the researchers listed below. They may be shared with other researchers to assist with testing. They will not be sold. Some of the storage and testing of your samples for research will happen locally in Tanzania or Uganda, and some will happen in the United States. The samples will be stored forever, unless you tell us to destroy them.
- You will be asked to provide a sputum sample.
  - The sputum will be used to check for the *Mycobacterium tuberculosis*, the germ that causes tuberculosis (TB).
  - The tests will be performed at the hospital. Results will be given to you and your doctors.
- If the blood tests show that you are not HIV-positive, or if you have an allergy to TB medicines or other medicines that interact with the study drugs, you will not be able to participate in the study, but you will be referred to a doctor at this hospital for any additional medical care.
- You will receive the first round of 28 days' worth of sepsis treatment, according to the study group that you were randomly assigned, at no cost to you.

<u>#2 Enrollment study day 2:</u> (if you are on TB treatment)

1. You will have your blood drawn by a nurse/doctor at four (4) timed intervals (hour-1, 2, 6, 12) after you take your anti-TB medication. This blood will be used to check the amount to anti-TB medication that is in your blood. These tests will be performed in a specialized research laboratory.

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#3 In-person follow-up visits (1 week, 2 weeks and 3 weeks into TB therapy)

1. You will be asked some questions, including any current symptoms and medications.
2. We will document your vital signs, height and weight and perform a physical exam.
3. You will be asked to provide a blood sample. The blood may be used to measure the levels of the TB drugs in the body and your blood counts, liver function and kidney function. The tests will be performed in the hospital and the research laboratory.

#4 Final follow-up phone call (no longer than 6 months into TB treatment)

1. We will communicate with you via telephone to ask you some questions about your health.

Could the research hurt me?

Sometimes things happen to people in research studies that may hurt them or make them feel bad. These are called risks. The risks of participating in this study include:

1. Medications given in this study may cause side effects. Participants who are randomly assigned to receive standard or sepsis-specific TB medicine may experience the following common symptoms including, but not limited to nausea, vomiting, abdominal pain, and nerve damage that causes a loss of sensation or movement in part of the body. A less likely, yet more serious side effect includes liver damage. Doctors will monitor all patients' liver health regularly and will provide treatment for any symptoms as needed, including taking away the study drug, if necessary.
2. Pain or discomfort from the needle stick used for blood draws. Sometimes this can lead to bruising. Very rarely, an infection can develop where the blood is taken. This is no different than routine medical care. In order to minimize the chances of these risks, only experienced nurses and/or doctors will be asked to do this procedure.
3. Loss of confidentiality: We will take great care to protect your information by using it only for our research purposes. Only a part of the research team will have access to information such as your name; this information will be kept in a locked and secure location and will not be released to others outside the team.

(For female participants) If you are pregnant or think you might be pregnant, please tell us so we can talk about this with you.

Could the research help me?

People also might have good things happen to them because they are in research studies. These are called benefits. The benefits to you of being in this study might be:

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1. Getting additional test results such as the blood counts and urine results.
2. Additional medical attention that you receive from the research team (nurse/doctor), including additional education about the nature of sepsis, HIV and/or TB disease and how it impacts you and your family.
3. Participants who receive TB medicine may have improved health outcomes at the 28 days and 6 month marks. All participants are likely to have urine- and sputum-based TB tests performed more quickly than people who do not participate in the study.
4. The study could help doctors in other areas of the country (and around the world) where HIV and TB are widespread, to learn how to better treat patients who have sepsis and improve their chances of surviving the disease.

The doctor and/or the researcher will inform you of any relevant information found from the conduct of this study that is important to your personal medical care or situation.

How will my privacy be protected?

Study records that identify you will be kept confidential as required by the regulatory authorities in Tanzania, Uganda and the United States. If you sign this consent, you agree to allow the researchers to use and disclose health information about you to conduct this study. If required by the National Institutes of Health (NIH), these individuals or their designees may also release your medical records, the consent form associated with this study, this authorization and the information about you created by this study to NIH or their designates. In addition, the information created about you may be shared with other institutions doing this study. Other persons who may have access to your records include groups such as data and safety monitoring boards which oversee the safety of a study including accrediting agencies, or Tanzania, Uganda and United States federal, state and local agencies having oversight over this research.

The researchers leading this study include Dr. Stellah Mpagama, Dr. Conrad Muzoora, Dr. Tania Thomas, Dr. David Boulware, Dr. Christopher Moore, Dr. Scott Heysell and their staff (researchers associated with their staff and Kibong'oto Infectious Disease Hospital, Mbarara University of Science and Technology, the University of Minnesota and the University of Virginia).

If you sign this form, you have given us permission to release information to these other people. There is no expiration date to this permission. If you decided to withdraw your permission and end this agreement to release the information collected about you, please contact Dr. Stellah Mpagama, Kibong'oto Infectious Diseases Hospital, Mae Street, Lomakaa

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Road. Siha – Kilimanjaro, Tanzania (phone number: +255 272 97141), or Dr. Conrad Muzoora, Mbarara University of Science and Technology, Mbarara, Uganda (phone number: +256 772 547175). They will help you document in writing your decision to withdraw this permission. Please note that any information already obtained will continue to be used.

Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. There is potential that information released to the NIH or governmental agencies may be released again and would no longer be protected by privacy laws.

Your participation in this research study is voluntary. However, you will not be allowed to participate in this research if you do not sign this form.

Will I be compensated for my participation?

We will provide travel reimbursement and meals for the follow-up visits. Study participants who complete the week 28 visit will be compensated with one year's worth of health insurance.

Do I have to participate?

You do not have to be in this study if you do not want to. This means your participation is voluntary. It is up to you to decide whether or not being in the study is in your best interest.

You can also stop participating in this study at any time. Any information gathered about you before you decide to stop this study will continue to be used. If you decide to stop, no one will be angry or upset with you. No one will treat you differently if you decide not to be in this study. Any new findings that develop during the course of the study which may impact your willingness to continue in the study will be shared with you. Your participation in the research may be stopped by the study team without your consent if your continued participation in the study is not thought to be in your best interest.

If I don't want to participate, what other choices do I have?

The only alternative is to not participate in this study**. You will still receive all the medical care necessary to manage your sepsis.**

Who can I contact with questions about my rights as a research subject?

Uganda National Council for Science and Technology
P.O. Box 6884
Plot 6, Kimera Road, Ntinda
Kampala, Uganda

Telephone +256 414 705500)

National Health Research Ethics Review Committee
National Institute for Medical Research
2448 Ocean Road
P.O. Box 9653, Dar es Salaam, Tanzania
Tel: +255 22 2121400
Fax: 255 22 2121360
Website: www.nimr.or.tz

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908 USA
434-924-2620
irbhsr@virginia.edu

Who can I contact with questions about this study?

Dr. Stellah Mpagama, Kibong'oto Infectious Diseases Hospital, Mae Street, Lomakaa Road. Siha – Kilimanjaro, Tanzania, +25527297141 (tel), +255754860576 (mobile), sempagama@yahoo.com or sempagama (Skype)

Dr. Conrad Muzoora, Mbarara University of Science and Technology, Mbarara, Uganda, +256 772 547175 (mobile), conradmuzoora@gmail.com (email) or conrad.muzoora (Skype)

Dr. Christopher Moore, University of Virginia, PO Box 801340, Charlottesville, Virginia, USA 22908-1340, +1-434-924-9678 (office) or ccm5u@virginia.edu

Dr. Scott Heysell, University of Virginia, PO Box 801340, Charlottesville, Virginia, USA 22908-1340, +1-434-243-9064 (office) or skh8r@virginia.edu

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Signatures

Please ask as many questions as you need to make sure you understand the study before you sign this form.

_____	_____	_____
PARTICIPANT'S NAME (SIGNATURE OR THUMB PRINT)	PARTICIPANT'S NAME (PRINT)	DATE

_____	_____	_____
SURROGATE CONSENTER'S NAME (SIGNATURE)	SURROGATE CONSENTER'S NAME (PRINT)	DATE

_____
(RELATIONSHIP TO PARTICIPANT)

If the potential participant is unable to sign and date the informed consent form but has delegated decision-making authority to a surrogate consenter, the surrogate must sign and date the lines above and indicate their relationship to the potential participant. Otherwise, leave these lines blank.

_____	_____	_____
INTERPRETER'S NAME (SIGNATURE)	INTERPRETER'S NAME (PRINT)	DATE

If an interpreter was used to explain this study to a potential participant, then the interpreter must sign and date the lines above. Otherwise, leave these lines blank.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE