CONSENT FORM

Protocol Name:	**Reversing Tissue Fibrosis to Improve Immune Reconstitution in HIV**	
Site:	**University of Minnesota**	
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You are invited to be in a research study that looks at the use of a medication that may slow down HIV infection in the body. The study's purpose is to find out if the medication makes HIV infected people who are already on HIV medicines healthier.

This medication is called losartan and is approved by the Food and Drug Administration (FDA), but not for treatment of HIV infection. Losartan is commonly used to treat high blood pressure. However, this medication may help to limit the damage that HIV causes in the body.

You were selected as a possible participant because you have an HIV infection that is relatively well controlled. Some factors that could make you ineligible for this study include low blood pressure, chronic inflammatory disease, and liver or kidney disease. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted at the University of Minnesota by Dr. Timothy Schacker from the department of infectious diseases, and is being sponsored by the National Institutes of Health. The pharmaceutical company, Merck, will be supplying the study drug. Fifty HIV infected subjects will be enrolled in this study.

Background Information:

Research has shown that HIV copies itself mostly in lymphatic tissue. These tissues are sometimes referred to as nodes and are found throughout the body. For example, tonsils are part of the lymph system.

The lymph cells in which HIV copies itself most are called CD4 cells. HIV can infect CD4 cells that are either resting or "active," but copies itself well only when it enters an "active" CD4 cell. When HIV copies itself in them, it destroys these cells. When CD4 cells are destroyed, it makes people infected with HIV at risk of getting infections and cancers. This process is also related to inflammation and scarring

of healthy tissues. There seems to be a connection between presence of scarring and a smaller number of healthy immune cells to fight infection.

The purpose of this study is to find out if losartan, a non-HIV medication, can lower the amount of scarring and the number of "active" CD4 cells in the body of a person with HIV infection. Lowering the number of "active" CD4 cells means that fewer CD4 cells are "targets" for infection by HIV. The main questions we hope the study might answer are:

- Does the use of a commonly-used high blood pressure medication lower the amount of scarring in the lymph nodes (where CD4 cells live and work)?
- How do the CD4 cell death and growth rates change with the use of this medication during HIV infection?
- Does the use of a commonly-used high blood pressure medication lower the number of "active" CD4 cells that HIV can infect?
- Does the use of this medication boost your immune system to respond to vaccines?

None of the tests, vaccines, or procedures in this study is experimental. However, our testing of an FDA-approved non-HIV medication in the setting of HIV infection is experimental.

Procedures:

The study will last for 30 months. If you agree to be in this study, we would ask you to do the following things.

You will be asked to provide some information about your current health conditions, medications you are currently taking, and data such as your age, date of birth and ethnic origin.

You will be randomized (like flipping a coin) to receive either losartan or a placebo (sugar pill). The study will supply both. The study will be double-blinded, which means that neither you nor the research investigators and staff will know if you will receive the study drug or the placebo.

For the 30 months of the study, you will take 1 pill of the study drug, once each day. If you are tolerating the drug, we will increase the dose after the first 14 days. At 30 months, you will stop taking the drug. We ask that you bring your pill container and any unused medication to each clinic visit so we can keep track of how many doses of the medication you have taken. At each visit after screening,

you will also be counseled about the importance of taking the study drug as prescribed.

After taking losartan for about two years, you will come for three visits for Gardasil vaccine injections to see if losartan boosts your immune system's ability to respond to vaccines.

Screening Visit: You will be asked to come to the University of Minnesota Health Clinical Research Unit where you will be asked to go through a screening process to make sure you are able to take part in the study. At the screening visit, you will undergo a health history and full physical exam. If study doctors are unable to obtain your original HIV antibody results, blood will be drawn to verify you have HIV antibodies. Blood will be drawn (about 2 tablespoons) to check your CD4 cell count and HIV viral load and to make sure your kidney, liver, and blood cells are healthy prior to starting one of the two study medications. Hepatitis C (HCV) testing will also be performed. Prior to this, study staff will talk with you about HCV, including how it is spread, how to protect yourself, and the testing process. Results will be available within 72 hours. If any tests are abnormal, you will be referred to an appropriate medical provider. Positive HCV test results will be reported to the Minnesota Department of Health. All women of childbearing age will have a pregnancy test, as a negative test is required prior to starting the study medications.

Day 0: You will be asked to come to the research unit where a medical history and targeted physical exam will be performed and blood samples will be collected (about 6 tablespoons). A biopsy (a sample of tissue) of a lymph node in your groin will be collected by a surgeon. A colonoscopy with biopsy will also be done by a doctor who specializes in this test. After these procedures you will be asked to rest in the research unit for at least 4 hours. While in the research unit, you will be given a supply of the study drug and will start taking it right away.

Day 7: We will call you to check on how you are feeling since starting the study drug.

Day 14: You will come to the research unit for a brief check up and to have blood drawn (about 1 ½ teaspoons).

Optional MRI Sub-study Visit: Within two weeks after the screening visit, an MRI visit will be scheduled. This MRI will occur at the Center for Magnetic Research (CMRR), this visit will last about 3 hours. During this visit, before your MRI, a portable ultrasound machine will be used to identify your lymph nodes that will be scanned and biopsied at a future visit. It is expected that you will only have one MRI visit. However, you may be asked to return for another MRI visit at a different magnet strength.

You will sign a separate consent form for this sub-study that will discuss the study procedures and risks associated with an MRI. The goal of the sub-study is to develop new ways to acquire and analyze MRI data to look at changes in the body between the normal and disease state. The MRI sub-study may involve imaging any part of the body from head to toe. If you do not want to participate in the MRI sub-study, you may choose not to sign the sub-study consent form. You may still participate in the main study if you wish.

Month 1: You will come to the research unit for a check up (which includes medical history and targeted exam) and will then be asked to stay for 12 hours and return the next day for a blood draw. Blood will be collected at 1, 2, 3, 4, 6, 8, 12, and 24 hours after you take a dose of your study drug and HIV medications to monitor medication levels in blood. About 15 tablespoons of blood will be drawn over the course of this visit.

Months 3, 6, 9, 15, 18, 21 and 27: Come to the research unit for a brief check up (which includes medical history and targeted exam) and to have blood drawn (about 6 tablespoons).

Month 12: Come to the research unit for a check up (which includes medical history and targeted exam) and blood sample collection (about 6 tablespoons). A biopsy (a sample of tissue) of a lymph node in your groin will again be collected and a colonoscopy with biopsy will also be repeated at this visit. After these procedures you will be asked to rest in the research unit for at least 4 hours.

Month 23: Come to the research unit for a check up (which includes medical history and targeted exam) and to have blood drawn (about 6 tablespoons). You will be given the 1st dose of the human papillomavirus (HPV) vaccine. This vaccine is also known as Gardasil. This is a shot that will be given into the muscle of your thigh. You will be monitored in the research unit for 30 minutes after the vaccine is given to make sure you don't have a reaction.

Month 25: Come to the research unit for check up (which includes medical history and targeted exam) and to have blood drawn (about 3 ½ tablespoons). You will be given the 2nd dose of the HPV vaccine in your thigh. You will be monitored in the research unit for 30 minutes after the vaccine is given to make sure you don't have a reaction.

Month 29.5: Come to the research unit for a check up (which includes medical history and targeted exam) and to have blood drawn (about 6 tablespoons). You will be given the 3rd dose of the HPV vaccine in your thigh. You will be monitored in the research unit for 30 minutes after the vaccine is given to make sure you don't have a reaction.

Months 30: This is the last scheduled study visit. You will come to the research unit for a check up (which includes medical history and targeted exam) and blood sample collection (about 6 tablespoons). A biopsy (a sample of tissue) of a lymph node in your groin will again be collected. A portable ultrasound machine will be used to identify this lymph node before the biopsy. You will also have a colonoscopy with biopsy. After these procedures are complete, you will be advised to stop the study drug. After these procedures you will be asked to rest in the research unit for at least 4 hours.

A total of about 81 tablespoons of blood will be collected over the 30 month duration of the study. At all visits except month 25, blood will be obtained to monitor the health of your blood cells, kidneys and liver. At all visits except Day 14 and Month 25, blood will also be obtained to monitor your HIV viral load and CD4 count.

For women of childbearing age, pregnancy testing will be performed at screening, baseline, every 3 months and anytime during follow up when the woman or investigator suspects a pregnancy.

You may choose to end your participation before the end of the 30 month study period. If you chose to end your participation early, we will ask that you return any study medication and for permission to contact you at the end of the 30 month period to check on your health status.

After all subjects have completed this study, you will receive information about which study drug you were receiving (either losartan or the placebo drug).

Explanation of Risks of Being in the Study:

The study has several risks. Questions about recent sexual activity may cause embarrassment. Anticipation of a medical procedure may cause stress or anxiety. Physical examination of the groin may be uncomfortable and cause embarrassment. Discussion of past medical history or risk factors for HIV infection may be stressful and cause anxiety. You may decline to answer any questions that you do not feel comfortable answering.

<u>Study Medication: Losartan</u>
This medication is approved by the FDA. Losartan is used to treat high blood pressure. The possible side effects of Losartan include dizziness, lightheadedness, headache, fatigue, cough, upset stomach, vomiting, diarrhea, sore throat, fever, sweating, fast heart rate, chest pain, weakness, anemia (low red blood cell count), allergic reaction and kidney damage.

This medication should not be used during pregnancy. If a developing fetus is exposed to losartan, injury or even death may result. For this reason, if you are a

woman of childbearing age, you will be asked whether or not you are sexually active and if you are, what type of birth control you use. You must be willing to use a reliable form of birth control such as birth control pills, intrauterine device (IUD), depo-provera, diaphragm, cervical cap with spermicide, or implant medication for the 30 month study period. Condoms cannot be the only form of birth control you use. If you become pregnant during the study or think you may be pregnant, you should inform either the Principal Investigator, Dr. Timothy Schacker, or a study nurse immediately. We will ask that you return any study medication and stop your participation in the study. We will ask permission to contact you at the end of the pregnancy to check on the health of you and the baby.

Although we do not expect that losartan will interact with any of your HIV medicines, this has not been well studied. For this reason, we will be measuring levels of losartan and your HIV medicines in your body regularly throughout this study. You will be informed if there are any interactions between these medicines.

Blood Sample Collection

The most common risks of blood sample collection are pain and infection at the puncture site, bruising, bleeding, a feeling of lightheadedness and possible fainting.

Human Papillomavirus 9-valent Vaccine, Recombinant (Gardasil), Merck & Co., Inc.

This vaccine is approved for use in men and women ages 9 to 26 to prevent disease related to certain strains of human papillomavirus (HPV). HPV is the virus that causes genital warts and cervical cancer. It is not approved for use in older individuals because it is not clear how well it would work in this group of people since many of them have already been exposed to HPV. However, there is no evidence to suggest that this vaccine is not safe for use in older people.

This vaccine will be injected into the muscle of your thigh.

The vaccine used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the medical staff at your site.

The following serious side effects have been associated with the use of Gardasil:

- Hypersensitivity (allergic) reactions, such as rash, fever, flu-like feeling, blisters, facial swelling, or even problems breathing. These reactions, in severe form, may be life threatening.
- Guillain-Barré Syndrome (a form of paralysis)

In addition to the serious side effects listed above, additional side effects include:

- Soreness, tenderness, itching, redness, bruising, or swelling at the injection site
- Headache
- Fever
- Nausea and vomiting
- Dizziness
- Fainting may occur after receiving the injection, which may result in falling with injury. Shaking, stiffening and other seizure-like activity have also been reported.
- Tiredness
- Chills

If after being injected with the vaccine, you become pregnant or think you may be pregnant, you should inform either the Principal Investigator, Dr. Timothy Schacker, or a study nurse immediately, so the study team can inform the company who makes the vaccine.

Lymph Node Biopsies

Lymph node biopsies of your groin will be done at the research unit. The actual surgery will only take 30-40 minutes but you will need to be there 6 hours. You should not eat or drink anything for at least 6 hours before surgery. The groin area will be scrubbed with an antiseptic solution. Local anesthetics (similar to Novocain) will be injected to numb the area. An incision between 1 and 3 inches will be made. The lymph node will be uncovered and removed. A lymph node is about the size of a peanut. The surgeon will close the wound with stitches, and then a bandage will be put over the wound.

After a period of at least 4 hours you will be allowed to leave the biopsy appointment. You will be asked to remain inactive until the next morning. You and the surgeon will discuss the use of a drug to relieve any pain. The entire procedure from the time you enter the hospital until you are discharged should be no longer than 8 hours.

Three days after the procedure you may be examined in the clinic. The wound will be examined and you will be asked questions about pain, drainage from the wound, or discomfort. If there is any sign of infection you will be referred back to the surgeon for another examination and a prescription of antibiotics or another appropriate treatment. The exact antibiotic will be chosen by the surgeon or investigator.

The surgeon will advise you as to the best way to manage stitches that are in place. He may ask you to come back to clinic 5-7 days after the procedure to have the stitches removed, or the stitches may be the dissolving type. You will be fully informed of which type you have.

The lymph node biopsy procedure may cause pain, even though you have been given an anesthetic. There may be bleeding associated with the procedure. There is the risk of infection, however it is less than 2 percent. There is the possibility you might develop a seroma, which is a collection of fluid under the skin and around the wound. There is the possibility that you may develop a scar at the site of your lymph node biopsy. You will most likely have pain after the lymph node biopsy. Occasionally, when we do a lymph node biopsy we cannot find the lymph node that was felt prior to the procedure. This is unlikely; however, it has happened.

Colonoscopies

A colonoscopy is a visual exam of the lining of the rectum and colon (large intestine) using a flexible tube with a tiny camera on the end. This instrument allows the doctor to view the inside of your rectum and colon and take a small piece of tissue from the small bowel. The bowel must first be cleared of all residue before the test. To do this, you will be asked to stop eating solid foods at 3pm the day before your procedure. It is okay to drink clear liquids such as Gatorade, broth, etc. At 5pm you will start to drink a gallon of a solution that will make you have bowel movements until your bowel is emptied. You should complete this by 10pm. You can continue to drink clear liquids until 6 hours before your appointment.

The colonoscopy will be performed at the University of Minnesota Medical Center, Fairview on the same day as your lymph node biopsy. You will lie on your left side or on your back during the exam. The doctor will insert the colonoscope into your rectum. The tube is about the size of an adult's forefinger. The colonoscope will be gently guided through your colon. The doctor will put air into your colon to see it better. This may make you feel full and crampy. Some of the air will be removed at the end of the exam. You may pass any remaining air. Twenty small tissue samples will be collected from your small bowel and large bowel during the procedure. These biopsies will not hurt.

The entire procedure usually takes less than an hour. There is little pain. However, mild sedation is given to relieve anxiety and discomfort. After the colonoscopy, there may be slight discomfort, which quickly improves with the expelling of gas. Most people can resume their regular diet later that day.

The most common risks associated with colonoscopy are: abdominal cramping, bleeding, anxiety, and a feeling of dizziness from the medications used to help you relax. A very rare complication of colonoscopy is perforation, or small hole, of the intestine.

Because you will be given sedating medications for the procedure, you will not be allowed to drive home at the end of the study day. We will arrange for transportation for you if needed.

If any abnormalities that may impact your health are found on physical exam, during the colonoscopy procedure or on analysis of tissue or blood samples, the research team will discuss this with you, provide you with a copy of the results, and, if you have signed a release of information, will discuss results with your primary doctor.

Benefits:

This research has the potential to benefit people infected with HIV but no direct benefit is assured by participating in this study. However, you will be provided with results of all clinical lab tests obtained during this study as well reports from your colonoscopies. If there are any abnormalities found on pathology review of your biopsy samples you will be notified of these results as well.

Compensation:

For your time and inconvenience related to your participating in this study, you will be paid the following amounts for each of the study visits you complete:

- Quarterly Blood Draw: 12 visits, $20 paid via Target gift cards, $240 total
- Inguinal Lymph Node Biopsy: 3 visits, $300 paid via check, $900 total
- Colonoscopy with Ileal and Rectal Biopsy: 3 visits, $300 paid via check, $900 total
- Month 1 visit: 1 visit, $130 paid via check, $130 total
- MRI Sub-study: 1-2 visits, $85 paid via check, $170 total if you are asked to come in for a second MRI.

All checks will be mailed to you 2-3 weeks after each visit, and Target gift cards will be given during the visit. The maximum amount you could receive by completing all of the scheduled study visits in the study is $2170, or if you also participate in the MRI sub-study, the maximum amount is $2255 ($2340 if you are asked to come in for a second MRI). You may be asked to come in for additional unscheduled blood draw visits.

If you receive more than $600 in a calendar year you may be required to report the compensation to the Internal Revenue Service (IRS).

Research-Related Injury:

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. The National Institutes of Health does not have a mechanism to provide compensation for research related injury. If you think that you have suffered a research related injury let the study physicians know right away. You are not giving up your legal rights by signing this consent form.

Confidentiality:

A Certificate of Confidentiality will be obtained for this study and records of this study will be kept private. In publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study may; however, be reviewed by the National Institutes of Health, the Office for Human Research Protections, the Institutional Review Board, by departments at the University of Minnesota, and other local, US, and international regulatory entities with appropriate regulatory oversight. To these extents, confidentiality is not absolute. Study data will be encrypted according to current University policy for protection of confidentiality.

Your insurance information may be collected at the time of check in for your research visits. If you have questions about what will or will not be billed to you, please ask your study team.

Information collected about you for research may be recorded in your medical record. If you do not have a medical record in the Fairview system, one will be created for you.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the web site will include a summary of the results. You can search this website at any time.

Any samples donated by you will be kept for up to 5 years for possible use in future studies. This is a requirement for study participation. The sample will be labeled with a tracking number that will allow the investigators to know who donated the specimen and when; however the specimen will not have any other information on it that might identify you.

Protected Health Information (PHI):

Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Voluntary Nature of the Study:

Your decision whether or not to participate will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships. You may be terminated from the study by the Principal Investigator to protect your safety or if you are unable or unwilling to comply with visits, study procedures, study medication or your HIV medicines. You will also be withdrawn if the study is stopped. In some situations, participants may be discontinued from the study medication but will continue follow up procedures. If you discontinue the study, you will be asked to return for an Early Termination visit at which time a medical assessment will take place and you will return any unused study drug. If you terminate the study you will be followed for 3 months to ensure that no complications of study participation develop and we may also contact you to check in at the end of the 30 month study period.

Alternatives to participating in this study:
The alternative to participating in this study is to decide not to be in it. Treatment can be obtained as a part of standard care from your physician.

New Information:
If during the course of this research study, there are significant new findings discovered which might influence your willingness to continue, the researchers will inform you of those developments.

Contacts and Questions:
The principal researcher conducting this study is Timothy Schacker, M.D. If you have further questions at any time regarding the trial or your rights as a trial subject, or if you have a trial related injury, you should contact him at (612) 624-9996.

To share feedback privately about your research experience, including any concerns about the study, call the Research Participants Advocate Line: 612-625-1650 or give feedback online at www.irb.umn.edu/report.html. You may also contact the Human Research Protection Program in writing at D528 Mayo, 420 Delaware St. Southeast, Minneapolis, Minnesota 55455.

You will be given a copy of this form to keep for your records.

Statement of Consent:
I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Signature of Subject	Date
Printed Name of Subject	Date
Signature of Person Obtaining Consent	Date