INSTITUTE: National institutes of Allergy and infectious Diseases

STUDY NUMBER: 14-I-0039 PRINCIPAL INVESTIGATOR: Irini Sereti, MD

STUDY TITLE: Elite Controller and ART-treated HIV+ Statin versus ASA Treatment Intervention Study (ECSTATIN)

Continuing Review Approved by the IRB on 04/23/18
Amendment Approved by the IRB on 09/25/18 (O) Date Posted to Web: 10/03/18
Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

THE PURPOSE OF THIS STUDY

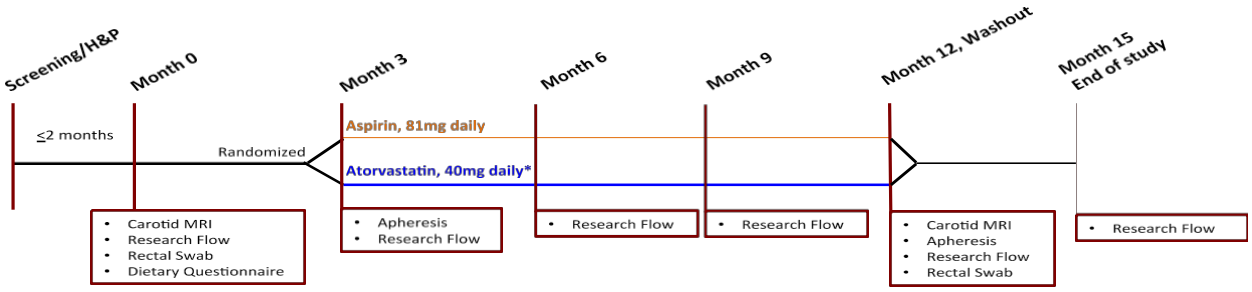
You are being asked to take part in this research study because you are infected with the human immunodeficiency virus (HIV) and have an HIV viral load (measure of the HIV virus in the blood) below the limit of detection and either: (1) you have never had to take anti-HIV medications (ARVs), have stable CD4 counts, and never had an opportunistic infection, or (2) you have been taking ARVs for 4 continuous years.

You are invited to participate in a study that will look at changes in the body's immune and clotting system markers. The immune system is made up of cells and substances that protect the body from infection and foreign matter. The activation of the immune system (or inflammation) can sometimes be harmful. Similarly, the clotting system is what makes the blood clot and protects us from bleeding but can be sometimes harmful if it is inappropriately activated.

In chronic HIV infection, there is increased inflammation and coagulation (clotting) that may put people at higher risk for cardiovascular diseases such as stroke or heart attacks. Our goal is to study how immune and clotting system markers may change in people infected with HIV after receiving 9 months of a daily dose of aspirin (a medication that decreases clotting and inflammation) or atorvastatin (a medication which lowers blood cholesterol and decreases inflammation). As part of the study we will also examine your carotid vessels (the major blood vessels that supply blood to the neck and head) by magnetic tomography to look at the thickness of the vessel wall.

A total of 80 people will be enrolled in the study. There will be 40 volunteers in each category. Half of the volunteers in each category will be randomized (process similar to the toss of the coin) to either a once daily dose of aspirin or a once daily dose of atorvastatin. Each group will receive 9 months of the medication. Volunteers in each group will have a 3 month observation period before and after treatment. The total duration of the study for each volunteer will be 15 months.

Study Procedures and Timeline:



* ATV will be dose adjusted for subjects on ART regimens with significant interactions.
**PBMCs, Serum, Plasma, Safety Labs, and Fasting Lipid Profile will be collected at each study visit.

STUDY PROCEDURES

Medication Administration

Both aspirin (81 mg tablet daily) and atorvastatin (40 mg tablet daily, dose adjusted for subjects on antiretroviral regimens with significant interactions) are 2 FDA approved, well-studied and well-tolerated drugs known to decrease immune activation (inflammation) and prevent cardiovascular events (strokes and heart attacks) with minimal side effects. Study administration of both aspirin and atorvastatin are at dosages with limited risk for side effects.

Risks Associated with Aspirin and Atorvastatin

Risks associated with aspirin include increased risk of bleeding, particularly for people who consume 3 or more alcoholic drinks a day, clotting abnormalities, stomach pain, heartburn, nausea, vomiting and bleeding of the stomach and gastrointestinal track. Aspirin can also cause irritation of the stomach lining. Patients with kidney disease and liver insufficiency should avoid the use of aspirin. Aspirin should generally not be used in pregnancy. Aspirin has been known to cause birth defects and miscarriages in pregnant women.

Risks associated with atorvastatin include muscle damage and an increase in sugar in your blood. Atorvastatin can increase blood levels of liver enzymes, and should not be used in patients with chronic liver disease and in those who consume large amounts of alcohol. Fatal liver failure has been reported in patients on atorvastatin. Atorvastatin is not to be used in pregnancy due to significant risk of injury to the fetus.

Risk associated with medications in pregnant and breastfeeding women

Due to the risk associated with these medications if taken during pregnancy, you must agree not to become pregnant during this study. Women of childbearing potential will have a pregnancy test before starting the study drugs and at each study visit. Because of the risk involved, you and your partner must use 2 methods of birth control, one of which must be a barrier method. You must continue to use both methods until the last study visit (Month 15). If you become pregnant while taking study drugs, the study drug will be discontinued immediately and you will be referred to a maternal fetal medicine specialist. You will be followed by the study team for the remainder of the study period or until you deliver the baby, whichever occurs later. You must contact us immediately if you think you might be pregnant.

Due to the potential for risk to a nursing infant if a mother is receiving either of the study drugs, breastfeeding should be discontinued while the mother is taking the study drug.

Apheresis

As part of this study, apheresis will be performed at Month 3 and Month 15 in those subjects deemed eligible for the procedure. In automated apheresis, blood is removed through a needle in the vein of one arm, spun in a machine which allows separation of the blood parts (usually white blood cells and plasma) needed for research, and then the remainder is given back to the patient through a needle in a vein in the other arm. A blood thinner is usually added to the blood while in the machine to prevent it from clotting during this processing.

The goal of these procedures is to allow the investigator to get a larger number of white blood cells than by simple blood drawing for study in the laboratory. Similar procedures are used in the Blood Bank of the Clinical Center to obtain blood products from healthy, non-study donors and as a form of therapy for certain diseases. The procedure will take approximately 60 to 90 minutes depending upon the amount of blood that is being collected and will be done at the beginning of the study and approximately at 9 months after starting the study drug (aspirin or atorvastatin). You have the right to refuse any apheresis procedures at any time.

Risks Associated with Apheresis Procedure

The risks associated with these procedures are mostly those of putting an intravenous line (a catheter placed into a vein) and are discomfort or pain at the site, occasionally bruising under the skin where the needle was placed, a lump at the

needle insertion site (hematoma), a tingling sensation during the procedure that can usually be relieved by chewing a calcium-containing tablet (such as Tums®), and rarely infection, and possible fainting. The intravenous line with flowing saline solution will be kept in place during the manual apheresis procedure. Other uncommon side effects of the procedure include anxiety, chills, pain, and lightheadedness. There may also be a slightly increased bleeding tendency for a few hours after the procedure due to the use of the anticoagulant (blood thinner). In addition, there are potential risks from re-infusion (giving back) of the blood after processing by the machine such as infection or a bad reaction to the blood parts. Very rarely, there can be blood vessel or nerve damage at the needle injection site, Finally, if the machine malfunctions, you may not have the blood returned to you, so it will be as if you had a large amount of blood drawn. In that event, the research blood draws of the protocol will be appropriately adjusted and you may have an additional blood count checked for your own safety. However, these risks are rare at our facility, since they have not been seen in many thousands of volunteers who have undergone this or similar procedures to date.

Rarely the performance of frequent apheresis procedures over a short period of time can result in a drop in total lymphocyte counts (white blood cells), including the absolute CD4+ T cell count, or a drop in the platelet count (platelets are the blood cells that help your blood to clot). The extent or duration of the drop in these counts may be unpredictable and vary from person to person, although we plan to monitor your counts during participation so that this is less likely to occur. The short or long-term risks associated with these drops are also unknown, although they could possibly be more serious in those individuals whose starting counts are already below the normal range as a result of HIV-1 infection or other medical conditions. We may limit the number of times that you are eligible to undergo apheresis over a set period of time, and may require that these or other safety blood studies be performed and checked periodically during the time that you are enrolled on this protocol. The time and volume of blood drawn each time you undergo this procedure will be determined by the study team and will strictly follow the clinical center guidelines for this procedure.

Magnetic Resonance Imaging (MRI) of Carotids

Magnetic Resonance Imaging (MRI) is a way to visualize the vascular walls of the major blood vessels to the neck and the head. It can detect build up of plaques and narrowing of vessel walls. It can potentially monitor worsening of vascular diseases. For this procedure, you will lay flat in a long metal cylinder as the machine makes images of the vessels.
If you are found to have abnormalities on the MRI, the findings will be reviewed with you in detail by the study team. This will include any clinical recommendations for future care or follow-up testing, and this information will also be provided to your doctor(s) when indicated.

Risks Associated With MRI

For most volunteers, the risk of the MRI will be discomfort. You will be asked to lie still for a long period of time. The machine makes a clicking sound, which many people find disturbing. The technician can give you special ear phones to quiet the nose. Volunteers with pacemakers, aneurysm clips, metallic prostheses, shrapnel fragments, welders and metal workers are at risk for injury and will be excluded from having the MRI performed.

Rectal swab and dietary questionnaire

We will be collecting a small sample of stool from your rectum. This will be done by inserting a small cotton swab (Q-tip) into the rectum. We will also be collecting information about foods and beverages that you have consumed.

Risk of rectal swab

You may experience pressure as the swab is inserted into the rectum, but the test is usually not painful.

GENETICTESTING

Some of the blood drawn from you as part of this study may be used for a test of genes that code for the immune system. Genes are pieces of DNA. DNA serves as nature's code (instructions) for protein production in the body. We will also check you for HLA type, which is a genetic test of markers of the immune system. It is usually used in matching for bone marrow or organ transplants. For research, HLA testing will be used to try to identify factors associated with the rate of progression of HIV disease or related conditions. Some HLA types have been associated with an increased risk of certain diseases like arthritis and other rheumatologic problems. However, simply having those HLA types doesn't mean you will develop these diseases.

In general, genetic testing may tell researchers something about how health or illness is passed on to you by your parents or from you to your children. When thinking about whether or not to participate in genetic studies, you should consider the possible effects on your emotional well-being. In other words, how might you feel about yourself and your life if you learn information about risks that could affect your own health or that of your children? In some cases, there may be no treatment. This could cause stress, anxiety, or depression. Additional genetics counseling and advice is available from NIH to help you understand the nature and implications of findings about you and your family. Also, relationships with other family members may be affected by finding out risks they have but did not want to know. An example would be if your children, brothers or sisters find out they have risks for health problems because of information found out about you.

Any genetic information collected or discovered about you or your family will be confidential. Results of HLA testing will become a part of your medical record at NIH. Medical records containing this information are maintained in a secured manner. Genetic information about you will not be revealed to others, including your relatives, without your permission. We will not release any information about you or your family to any insurance company or employer unless you sign a document allowing release of information. There may be a risk that genetic information obtained as a result of participation in research could be misused for discriminatory purposes. However, state and federal laws provide some protections against genetic discrimination. Researchers who will have access to genetic information about you will take measures to maintain the confidentiality of your genetic information.

Phlebotomy

Possible complications from drawing blood (venipuncture) include pain or bruising at the site of the blood draw, feeling lightheaded, a lump at the needle insertion site (hematoma), fainting, and rarely, infection. During each venipuncture, approximately 3 to 10 tablespoons of blood will be obtained (15 to 150 mL of blood). The amount of blood drawn will not exceed 37 tablespoons (550 mL) in an 8-week period, which is within the safety guidelines set by the Clinical Center of the NIH.

SCHEDULE OF VISITS AND PROCEDURES

Screening Visit

- Medical history that will include a review of your medical record and questions about current and past medications and illnesses
- Complete physical examination
- Blood and urine test to assess the function of your liver, kidneys and your HIV infection status

- Additional testing for HIV viral load, blood clotting, inflammation, hepatitis viruses, and lipid problems
- Women will undergo urine or blood testing for pregnancy

Baseline Visit and Months 3, 6, 9, 12, and 15
- Physical exam, medical history and medication history
- HIV Viral load and CD4+T cell count
- Blood and urine test for liver and kidney function, pregnancy testing, diabetes and lipid profile
- Additional testing for HIV viral load, blood clotting, inflammation, hepatitis viruses, and lipid problems

Baseline Visit and Month 12 Visit Only
- MRI of carotids
- Rectal swab and dietary history questionnaire. Dietary questionnaire at Baseline Visit only.

Months 3 through Month 9 Visits Only
- Daily aspirin or atorvastatin administration

Month 3 and Month 12 Visit only
- 1 liter apheresis or 30 mL blood collection

STORED SAMPLES AND FUTURE RESEARCH

Stored Samples and Future Research

If you agree to participate in this study, you also agree to let us store your samples for future research. These stored samples may help us learn more about HIV or other health problems. We will label your stored samples with information with a code that only the study team can link to you. We will keep any information that can be traced back to you as private as possible. If you change your mind and decide you do not want us to store your samples, please contact us. We will do our best to comply with your request, but cannot guarantee that we will always be able to destroy all your samples.

We might send your samples to other investigators for their research, without any information that can identify you. We might also share information such as your sex, age, health history, or ethnicity. We will not sell your samples and you will not be paid for any products that result from the research. Some future studies may need health information (such as smoking history or present health status) that we don't already have. If so, our study team will contact you. Future research that uses your samples will probably not help you, but it may help us learn more about how to treat or prevent HIV and other health problems. In general, the research tests we perform are not like routine medical tests, and may not relate directly to your medical care.

Risks Associated with Stored Samples

The greatest risk associated with storing samples is that someone may take information from your medical records without your permission. The chances of this happening are very low. If this information becomes available, you may face discrimination when you apply for insurance or a job. You may also have similar problems if you share the information yourself or let us release your medical records.

BENEFITS

Participation in this study provides no direct benefit to you. You will receive information about your health from the screening tests and physical exam. The results of the imaging of the carotids will not be provided until the end of the study. In the future, it is possible that information learned from this study may help HIV-infected persons at risk for heart disease.

ALTERNATIVES

Participation in this protocol is voluntary. You can choose not to participate in this study, and you can choose not to allow HIV, hepatitis or genetic testing or storage of blood, in which case you would not be eligible for further participation in the protocol.

COSTS TO YOU FOR YOUR PARTICIPATION

There will be no charge to you or your health insurance company for any of the costs that are directly related to this study.

COMPENSATION

You will receive $150 for each attempted or completed 1 liter apheresis procedure. If you are ineligible for the apheresis procedure, you will be compensated $40 for an additional blood draw of 30 mL (2 tablespoons). You will also receive $150 for each MRI; $70 for the dietary questionnaire and $30 for the rectal swab; $60 for each clinic visit with blood draw. At the End of Study Visit, volunteers will receive and additional $200 if all protocol study visits have been completed. You will be compensated for travel according to the NIAID/NIH travel policy.

CONFLICT OF INTEREST

The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf. You may ask your research team for additional information or a copy of the Protocol Review Guide. This protocol may have investigators who are not NIH employees. Non-NIH investigators are expected to adhere to the principles of the Protocol Review Guide but are not required to report their personal financial holdings to the NIH.

POLICY REGARDING HIV TESTING

As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS, in order to confirm your diagnosis for participation in the study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. **Payments.** The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. **Problems or Questions.** If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Irini Sereti, MD, Building 10, Telephone 301-496-5533 or the Study Coordinator, Dorinda Metzger, RN at 240-669-2962.

You may also call the Clinical Center Patient Representative at (301) 496-2626.

5. **Consent Document.** Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian Date Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM APRIL 23, 2018 THROUGH APRIL 22, 2019.

Signature of Investigator Date

Print Name

Signature of Witness Date

Print Name