Title of Research Study: CSC01: High Intensity Lipid Lowering for Coronary Artery Disease Prevention among Persons Living with Human Immunodeficiency Virus (HILLCLIMBER) Trial

Principal Investigator: Matthew Feinstein, MD

Supported by: This research is supported by Northwestern University

Protocol Version: 4.0, March 15, 2017

Financial Interest Disclosure: The following disclosure is made to give you an opportunity to decide if this relationship will affect your willingness to participate in this research study:

If your doctor is also the person responsible for this research study, please note that he is interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with another person who is not part of the research team before deciding whether to participate in the research.

Key Information:
The first few pages of this document include a summary of this study to help you decide whether or not to participate. Detailed information is provided after the summary.

Why am I being asked to take part in this research study?

We are asking you to take part in this research study because you are infected with the human immunodeficiency virus (HIV), the virus that causes AIDS, you are taking HIV medications, and you have heart disease (such as a heart attack) or are at high risk for heart disease.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

Heart disease is common among people with HIV. Statins are a group of medicines used to lower the levels of cholesterol (fat in the blood) that people make and to prevent heart-related disease events such as heart attacks.

In the general population, high dose statin medications are the standard of care for people who have had heart attacks, or are at high risk for heart attacks, because high intensity statin dosing decreases the risk for death and another heart attack compared with lower intensity statins. However, for people living with HIV, there have not been studies looking at high intensity statin doses due to concerns

regarding safety of these statins for people taking HIV medications. It is reassuring that trials of medium intensities of statins have generally shown good safety and tolerability for people with HIV taking HIV medications. At this point, though, we still do not know whether or not the potential added benefit of a higher intensity of statin preventing heart attacks is worth the potential safety risk of increasing the dose.

Rosuvastatin is a high intensity statin that is approved by the US Food and Drug Administration (FDA) for lowering blood cholesterol and preventing heart attacks and strokes in people at high risk for these events. Rosuvastatin has been shown to be safe in its lower dose range (moderate intensity) but has not been studied at its higher dose range (high intensity) – the dose used for people with heart disease in the general population – for people with HIV. Rosuvastatin was chosen for this study because there are thought to be few interactions between rosuvastatin and most commonly used HIV medications. For the comparison arm, we will use pravastatin, a lower intensity statin that is commonly used for people with HIV due to few potential interactions with common HIV medications, but is less effective at preventing first and recurrent heart attacks than higher intensity statins.

The main purpose of this clinical trial is to see if rosuvastatin at higher doses (20 to 40 mg daily) is more effective than pravastatin 40 mg daily at reducing blood cholesterol in people with HIV who have had a heart attack or are at high risk for heart attacks. We will also study the safety of high dose rosuvastatin compared with pravastatin 40 mg daily.

How long will the research last and what will I need to do?

We expect that you will be in this research study for 14 weeks. More detailed information about the study procedures can be found under the section **What happens if I say "Yes, I want to be in this research"?**

Is there any way being in this study could be bad for me?

This research may hurt you in the following ways:

The drug 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 this drug. 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.

Risks of Rosuvastatin

- Muscle problems. Rosuvastatin can rarely cause serious muscle problems that can lead to kidney problems, including kidney failure and rarely, death.
- Liver problems. Rosuvastatin can rarely cause liver problems that may rarely be serious. Your study nurse or doctor will do blood tests to check your liver before you start taking Rosuvastatin and while you take it.
- Diabetes mellitus. Increases in blood sugar have been observed in patients treated with rosuvastatin. In some cases these increases may exceed the threshold for the diagnosis of diabetes mellitus, primarily in patients already at high risk for developing diabetes.
- Be sure to let your doctor or study nurse know immediately if you develop any of these problems:
    - Persistent weakness, muscle tenderness, or pains that happen without a good reason, especially if you also have a fever or feel more tired than usual.
    - Nausea and vomiting.
    - Passing brown or dark-colored urine.
    - Feeling more tired than usual.
    - Noticing the skin and whites of your eyes become yellow.

- Having stomach pain.

Risks of Pravastatin

- Muscle problems. Pravastatin can, in rare circumstances, cause serious muscle problems that can lead to kidney problems, including kidney failure and rarely, death.
- Liver problems. Pravastatin can occasionally cause liver problems. Rarely are these liver problems serious. Your study nurse or doctor will do blood tests to check your liver before you start taking Rosuvastatin and while you take it.
- Be sure to let your doctor or study nurse know immediately if you develop any of these problems:
    - Persistent weakness, muscle tenderness, or pains that happen without a good reason, especially if you also have a fever or feel more tired than usual.
    - Nausea and vomiting.
    - Passing brown or dark-colored urine.
    - Feeling more tired than usual.
    - Noticing the skin and whites of your eyes become yellow.
    - Having stomach pain.

More detailed information about the risks of this study can be found under **"Is there any way being in this study could be bad for me? (Detailed Risks)"**

Will being in this study help me in any way?

Studies have shown statins to provide a benefit in terms of preventing heart disease in HIV uninfected patients with inflammation, but the effects of statins to prevent heart disease in HIV-infected patients is not known. If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. You may benefit from learning about your risk of a cardiovascular event, but it is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and cardiovascular disease.What happens if I do not want to be in this research?Participation in research is completely voluntary. You decide whether or not to participate. If you choose to not participate, there will be no penalty to you or loss of benefit to which you are entitled.

Instead of being in this study your choices may include:

- treatment with prescription drugs available to you
- treatment with experimental drugs, if you qualify
- no treatment
- continue routine medical care from your primary care provider

Please talk to your study doctor about these and other choices available to you. Your study doctor will explain the risks and benefits of these choices.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

Whom can I talk to?

If you have questions, concerns, complaints, or think the research has hurt you, please call the Bluhm Cardiovascular Institute main number at 312-695-4965 to have your study physician Matt Feinstein, MD paged. You can call this number anytime, including evenings and weekends.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). You may talk to them at (312) 503-9338 or irb@northwestern.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

How many people will be studied?

We expect about 40 people here at Northwestern will take part in this single-center study.

What happens if I say "Yes, I want to be in this research"?

Study visits

Before you can enter the study, you will need to come to the Infectious Diseases Clinic at 676 N. St. Clair to have evaluations done to make sure that you can take part in the study. This visit will last about 1 hour.

If you meet the eligibility requirements, you will return to the clinic within 45 days to enter in the study. If you enter the study, you will be seen in the clinic 5 times over the course of 14 weeks (plus the initial screening visit). The Entry visit will last about 1 hour and the Week 2, 6, 10, and 14 study visits will last about 30-45 minutes.

More details about the visits and procedures at each study visit are below.

If you leave the study early, or have to stop taking the study medication before the study is over, you will have the procedures listed in the table below.

If you do not enter the study

If you decide not to take part in this study after signing the consent form, or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, safety tests) information is being collected from you so that researchers may help determine whether there are patterns or common reasons why people do not join a study.Study treatment

If you enter the study, all participants will start treatment with:

Pravastatin 40mg daily for 2 weeks.

At the Week 2 study visit, the study treatment you will get will be chosen by chance (like flipping a coin):

High-intensity treatment (Rosuvastatin) OR

Moderate-intensity treatment (Pravastatin)

Neither you nor the study doctor will choose what treatment you get. You will have an equal chance of being given either treatment.

You will take the study medicine (either rosuvastatin or pravastatin) once a day, every day with or without food for 12 weeks (from study Week 2 to Week 14). The dose is 40 mg for pravastatin and 20 mg for rosuvastatin. If you are assigned to the rosuvastatin group, your dose will be increased to 40

mg unless if the Week 6 laboratory results and clinical assessment show that it is not safe to increase your dose.

Study procedures

The study staff can answer any questions you have about individual study visits and the procedures. The table below can be used as a quick reference, along with the explanations that follow.

Procedure	Screening	Entry	Week 2	Week 6	Week 10	Week 14 or discontinuation
Informed Consent	X					
Medical and Medication History	X					
Clinical assessment, including vital signs	X	X	X	X	X	X
Heart disease risk assessment	X					
Health and medicine assessment	X	X	X	X	X	X
Fasting Blood tests	X	X	X	X	X	X
(Pregnancy test)	X	X				X
Pills dispensed		X	X	X	(X**)	

X** If on rosuvastatin, dose is increased to 40 mg

Explanation of study procedures:

Clinical Assessment

You will have a physical exam at screening. At other visits, the extent of the exam will depend on how you are feeling at that visit. You will have vital signs taken, including, temperature, blood pressure and pulse. You will have measurements taken of your height and weight at entry. You will be asked questions about your health, side effects to the study drugs, and medicines that you are taking at every visit.

Your medical history and the results of your CD4 T-cell count (how many infection fighting cells are in your blood) and HIV viral load (how much HIV is in your blood) that were obtained from routine care will be collected. These tests will not be done through this study.

Heart disease risk assessment

At screening we will ask you questions about your cardiovascular disease history. You will also be asked about cardiovascular risk factors including your family history, smoking, alcohol use, and substance use.

Fasting Blood collected

Blood will be collected from a vein in your arm for safety reasons to evaluate your blood counts, chemistries, cholesterol (fat found in your blood), liver function, and kidney function at each visit (screening, weeks 0, 2, 6, 10, and 14). You will be told the results of these tests.

Additional blood will be collected to measure study drug levels (weeks 2, 6, and 10) and for storage for possible future testing for studies of the HIV virus and markers of inflammation and heart disease (weeks 0, 2, 14). Up to 15 mL of blood (approximately 1 tablespoon) will be collected at screening.

weeks 6 and 10. Up to 70 mL of blood (approximately 5 tablespoons) will be collected at weeks 0, 2, and 14.

Before the screen and all clinic visits you should not eat or drink anything, including food, beverages, candy, or gum for 8 hours before your visit. You can drink water before your visits. If you are not fasting we will ask you to return while fasting to have your blood drawn. Study staff may contact you by phone about fasting visits and dosing.

Discontinuation of Study Treatment

If you must permanently stop taking study-provided rosuvastatin or pravastatin before your study participation is over, the study staff will discuss other options that may be of benefit to you. You will be asked to return to the clinic to complete the discontinuation evaluations.

After you have completed your study participation, the study will not be able to continue to provide you with the rosuvastatin or pravastatin you received on the study. If continuing to take this or a similar drug would be of benefit to you, the study staff will discuss how you may be able to obtain the drug by prescription.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible to complete all study visits and procedures listed above.

What happens if I say "Yes", but I change my mind later?

You can leave the research at any time and it will not be held against you.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment.

If you stop being in the research, already collected data will not be removed from the study database. You will be asked whether the investigator ca collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Detailed Risks: Is there any way being in this study could be bad for me?

There is a risk of serious or life-threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risks of Rosuvastatin

- Muscle problems. Rosuvastatin can rarely cause serious muscle problems that can lead to kidney problems, including kidney failure and rarely, death.

- Liver problems. Rosuvastatin can rarely cause liver problems that may rarely be serious. Your study nurse or doctor will do blood tests to check your liver before you start taking Rosuvastatin and while you take it.

- Diabetes mellitus. Increases in blood sugar have been observed in patients treated with rosuvastatin. In some cases these increases may exceed the threshold for the diagnosis of diabetes mellitus, primarily in patients already at high risk for developing diabetes.

- Be sure to let your doctor or study nurse know immediately if you develop any of these problems:
    - Persistent weakness, muscle tenderness, or pains that happen without a good reason, especially if you also have a fever or feel more tired than usual.
    - Nausea and vomiting.
    - Passing brown or dark-colored urine.
    - Feeling more tired than usual.
    - Noticing the skin and whites of your eyes become yellow.
    - Having stomach pain.

Other problems that have been caused by rosuvastatin include headaches, rash (which rarely may be severe), severe allergic reaction or swelling, constipation, gas, diarrhea, pain or numbness in arms or legs, tendon rupture, urinary tract infection, dizziness, memory impairment, and depression. All of these problems are uncommon to rare.

Risks of Pravastatin

- Muscle problems. Pravastatin can, in rare circumstances, cause serious muscle problems that can lead to kidney problems, including kidney failure and rarely, death.

- Liver problems. Pravastatin can occasionally cause liver problems. Rarely are these liver problems serious. Your study nurse or doctor will do blood tests to check your liver before you start taking Rosuvastatin and while you take it.

- Be sure to let your doctor or study nurse know immediately if you develop any of these problems:
    - Persistent weakness, muscle tenderness, or pains that happen without a good reason, especially if you also have a fever or feel more tired than usual.
    - Nausea and vomiting.
    - Passing brown or dark-colored urine.
    - Feeling more tired than usual.
    - Noticing the skin and whites of your eyes become yellow.
    - Having stomach pain.

Other problems that have been caused by pravastatin include headaches, rash (which rarely may be severe), severe allergic reaction or swelling, constipation, gas, diarrhea, pain or numbness in arms or legs, tendon rupture, urinary tract infection, dizziness, memory impairment, and depression. All of these problems are uncommon to rare.

Risks of drawing blood

Taking blood may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting, or infection.

Unknown risks

Other side effects that are not known at this time could happen during the study. All drugs have a possible risk of an allergic reaction, which if not treated right away, could become life-threatening. During the study, you will be told about any new information that may affect your decision to stay in

the study. If you decide to stay in the study, you will be asked to sign an updated consent form. If you decide to leave the study early, the study staff will talk with you about your treatment options.

This study involves the use of your identifiable, personal information and there is a chance that a loss of confidentiality could occur. The researchers have procedures in place to lessen the possibility of this happening. See the section below titled: **"What happens to the information collected for the research?".**

What do I need to know about reproductive health and/or sexual activity if I am in this study?

Rosuvastatin and pravastatin risks to unborn babies are not well known. The research may also hurt a pregnancy or fetus in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death. You should not be or become pregnant or breastfeed while on this research study. If you are having sex that could lead to pregnancy, you must agree not to become pregnant.

If you can become pregnant, you must have a pregnancy test at screening and before you enter this study (1 teaspoon of blood or a urine specimen will be collected) and at any time that pregnancy is suspected. This test must show that you are not pregnant. If you become pregnant or think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices.

If you are sexually active, both men and women must use at least one accepted form of birth control while participating in this research study. You may choose from the birth control methods listed below:

- condoms, with or without a spermicidal agent
- a diaphragm or cervical cap with spermicide
- an IUD (intrauterine device)
- tubal ligation
- hormone-based contraceptive

Will it cost me anything to participate in this research study?

Taking part in this research study will not lead to any costs to you. The study will provide the study drugs, rosuvastatin and pravastatin, and all the tests and procedures that are done only for this research. Antiretroviral drugs (treatment for HIV) will not be provided by the study.

You and your insurance company will be charged for the health care services that you would ordinarily be responsible to pay. In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay.

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include learning of your own cardiovascular risk and possible prevention of heart disease. Studies have shown statins to provide a benefit in terms of preventing heart disease in HIV uninfected patients with inflammation, but the effects of statins to prevent heart disease in HIV-infected patients is not known. If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. You may benefit from learning about your risk of a cardiovascular event, but it is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and cardiovascular disease.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy.

We will do everything we can to protect your privacy. Any publication of this study will not use your name or identify you personally.

People who may review your records include the Office for Human Research Protections (OHRP) or other government agencies as part of their duties, Food and Drug Administration (FDA), Northwestern University IRB/EC (a group that protects the rights and well-being of people in research), study staff, study monitors, the drug company supplying the study drugs, and their designees.

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

Data Sharing

De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Can I be removed from the research without my OK?

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

- the doctor thinks it is in your best interest
- the study is cancelled
- you are not able to attend the study visits as required by the study

The study doctor may also need to take you off the study drug without your permission if:

- you are not able to take the study drug as required by the study
- continuing the study drug may be harmful to you
- you need a treatment that you may not take while on the study.
- you become pregnant

If you must stop taking the study drug before the study is over, we will ask you to continue to be part of the study and return for some study visits and procedures.

What else do I need to know?

This research is being funded by Northwestern University.

You will receive $50 cash for each of the 5 study visits for a total of $250 compensation, if you complete all of the visits.

If you need medical care because of taking part in this research study, contact the investigator and medical care will be made available. Generally, this care will be billed to you, your insurance, or other third party.

Injuries sometimes happen in research even when no one is at fault. Northwestern University does not have a program for compensation. There are no plans to pay you or give you other compensation for an injury or adverse event, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible.

What if we can no longer reach you during your study participation?

In the event you cannot be reached after multiple attempts to contact you, study staff may try to contact you through alternate phone numbers of family, friends, case manager, or acquaintances obtained at screening and updated at each visit. If you are unable to be reached through the alternate contacts we will attempt to obtain information about you from other sources such as family members, other designated contacts, or clinic records. The purpose of obtaining this information is to determine if you have died and the cause of death since last contact.

HIPAA Authorization

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Your health information we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history
- Lab tests, or certain health information indicating or relating to a particular condition as well diaries and questionnaires
- Records about study medication or drugs
- HIV testing results

During this study you may be coming to the Northwestern Memorial Healthcare Corporation (NMHC) entity (for example, Northwestern Memorial Hospital, Prentice Women's Hospital) for research appointments or to get clinical services, such as lab tests, needed for the study. When that happens, you will be scheduled for these services through the NMHC computer system. When a clinical exam or lab is done by NMHC or one of its employees for the purpose of this research study, that information will be kept in both NMHC's clinical records and in the study records.

The following groups of people may give the researchers information about you: All current and previous health care providers, including but not limited to the Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH).

Once we have the health information listed above, we may share some of this information with the following people. Please note that any research information shared with people outside of Northwestern University and its clinical partners (or affiliates) will not contain your name, address, telephone or social security number or any other direct personal identifier unless disclosure of the direct identifier is required by law [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigators office].

- Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for

Research Integrity and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study).

- Clinical affiliates, including but not limited the Northwestern Medical Group (NMG), and Northwestern Memorial Hospital (NMH). Your participation in this clinical trial will be tracked in an electronic database and may be seen by investigators running other trials that you are enrolled in and by your healthcare providers.
- Clinical affiliates, including but not limited to Northwestern Medical Group (NMG) and Northwestern Memorial Hospital (NMH), for purposes including, but not limited to, the affiliate's provision of care to you and/or the affiliate's scheduling of appointments and/or billing activities.
- Study monitors and auditors who make sure that the study is being done properly,
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS).

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Although you may revoke consent to participation in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing. To revoke your authorization, write to:

PI's Name: Dr. Donald Lloyd-Jones

Institution: Northwestern University

Department: Preventive Medicine and Medicine-Cardiology

Address: 680 N. Lake Shore Drive, Suite 1400, Chicago, IL 60611

You do not have to authorize the use or disclosure of your health information; however, you will not be allowed to take part in this research study. If you do not authorize the use or disclosure of your health information, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits.

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Signature of participant	Date
Printed name of participant	
Signature of person obtaining consent	Date

_____

Printed name of person obtaining consent