INSTITUTE: National Institute of Allergy and Infectious Diseases

STUDY NUMBER: 06-I-0197 PRINCIPAL INVESTIGATOR: Frank Maldarelli, M.D.

STUDY TITLE: A Randomized Placebo Controlled Trial of Atorvastatin in HIV Positive Patients Not on Antiretroviral medications with the Specific Aims of Studying the Effects of Atorvastatin on HIV Viral Load and Immune Activation Markers

Continuing Review Approved by the IRB on 4/14/08
Amendment Approved by the IRB on 03/20/08 (G) Date Posted to Web: 05/06/08
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.

Purpose of the Study

HIV, the virus that causes AIDS, grows in the immune cells of the body. Recent research has shown that for the HIV to multiply (replicate), it has to use some of the normal cell machinery. One of the pathways the virus uses to multiply requires cholesterol (a kind of fat in the blood). Laboratory research has indicated that if the amount of cholesterol in infected cells is reduced, HIV replication is also decreased. These experiments have been done only in the laboratory and it is not known whether reducing cholesterol in people infected with HIV will also reduce HIV replication. In this study we plan to investigate whether the use of cholesterol lowering drugs called statins will reduce HIV replication and lower the level of HIV in the blood. We are studying the effects of one statin called atorvastatin (Lipitor), which has been approved by the Food and Drug Administration (FDA) for treatment of persons with hyperlipidemia (elevated lipids in the blood). Atorvastatin is not an approved treatment for HIV infection, and should not be considered a therapy for HIV; even if it

does decrease HIV viral loads (the amount of the HIV virus in your blood), it is unlikely that atorvastatin alone will control HIV. Atorvastatin is approved by the FDA for the treatment of hypercholesterolemia and is available for use outside this study. However, atorvastatin is not FDA approved for treatment of HIV infection. As you are likely to have normal cholesterol you may not receive any benefit from taking atorvastatin. The desire to take atorvastatin should not be a reason for you to volunteer to take part in this study.

The primary purpose of this research study is to study the effect of this drug on HIV viral load. As part of this study we will be looking at:

- The amount of HIV virus in your blood (HIV viral load).
- The composition of the strain of HIV virus that you carry (HIV genotype).
- The response of your immune system to the virus.
- Some of your genes that may determine the way this drug may or not work against your strain of the virus.

Study Procedures

You have already come to the clinic for a screening visit, and have undergone testing to determine whether or not you qualify for the study. Based on your screening visit, you are eligible for the protocol and are invited to enroll in the study phase. In the study phase, you will be randomly assigned (by chance, like the flip of a coin) to one of two study groups. One study group will be asked to take atorvastatin, a medicine that reduces cholesterol and may affect the ability of your virus to multiply. The other study group will take a placebo (something like a sugar pill) that should have no affect either on the level of your cholesterol or the ability of your virus to multiply. Neither you nor your doctor will know whether you will be in the drug or to the placebo pill group. Once you have been assigned to either the drug or the placebo pill groups, you will remain in your groups/treatments for 8 weeks. Upon completion of 8 weeks, regardless of the study group you were in, you will be required to discontinue all study related medications for 4 weeks. There may be some circumstances where we may extend this off drug period to a total of 6 weeks. For instance, if you require the influenza vaccination, which can sometimes affect HIV-1 viral RNA levels, we will administer the standard inactivated vaccine at the beginning of the off drug period, followed by six week wash out. At the end of this period, you will be asked to switch your study assignments i.e. if you were on the placebo pill you will switch to the study drug atorvastatin and vice versa if you were on the study drug atorvastatin you will switch to the placebo pill. You will complete an additional 8 weeks on this assigned study treatment; after this you will stop all study related treatment and be observed for an additional 4 weeks.

While on this research study you will have regularly scheduled study visits; at these visits you will have blood drawn, symptoms assessed, physical examinations done, and a questionnaire given at regular intervals. You will be required to come fasting for these visits as we will be drawing blood to check the fats (lipids) in your blood. This test can vary depending on whether you are fasting or not. The blood will be used in standard as well as specialized tests. The standard tests will include tests to determine the health of your liver, kidney, muscles, blood cells and your pregnancy status as applicable. The specialized tests will include tests to determine the viral load (a measure of the amount of virus in your blood), study the effects of the drug on your immune cells, the genotype (tests to study the composition of your virus) and your own genes that might determine how the drug might, or might not work on you.

The table below details the number of visits, an estimate of the time you will be required to spend at each of the visits and the procedures you will undergo during these visits. The volume of blood drawn at each visit will be no more than 75 cc (about 4 tablespoons). This table is merely an approximation of what you can expect as a subject in this study, you may be required to undergo additional testing based on signs and symptoms that you may develop while on the study.

Week	**0 to 4**			**0**	**1**	**2**	**6**		**12**	**13**	**14**	**18**	**20**	**24**
Visit	**1**	**2**		**4**	**5**	**6**	**7**		**9**	**10**	**11**	**12**	**13**	**14**
Phase	**Screening**			**Study**										
Approximate time (hrs)	**2.5**	**30 min**	**30 min**	**2**	**45 min**	**45 min**	**45 min**		**2**	**45 min**	**45 min**	**45 min**	**2**	**1.5**
Procedure														
Consent process	X													
Clinical assessment	X			X	X	X	X		X	X	X	X	X	X
Questionnaire (fatigue scale)				X					X				X	
Physical exam	X			X					X				X	X
Blood draws	X	X	X	X	X	X	X		X	X	X	X	X	X
Atorvastatin or placebo				X	X	X	X		X	X	X	X	X	X

Study Population

We plan to enroll 22 subjects for this study and the anticipated duration on study for each subject is 30 weeks.

Summary of Entry Criteria

To participate in the study you must:

- Be greater than 18 years of age
- Be infected with the HIV-1 virus
- Off all Antiretroviral therapy (ART) "medicines taken to control the virus multiplication" for greater than three months prior to study entry. While of ART you must have a stable viral load "amount of virus in your blood".
- Be willing to use a method of contraception during the study period. Adequate methods of birth control include: condoms, male or female, with or without a spermicide; diaphragm or cervical cap with spermicide; intrauterine device; any of the methods that require a prescription (such as contraceptive pills or patch, Norplant, Depo-Provera, and others) or a male partner who has previously undergone a vasectomy,
- Be willing to have blood drawn
- Have no known allergy or contraindication to atorvastatin use
- Have the ability to understand and willingness to sign the informed consent
- Be willing to have blood stored for future testing including tests that will study your genes and the genetics of the virus
- Have a CD4 cell count "a measure of your immune cells" greater than 350 cells/ml
- Have three viral loads that average greater than 1000 copies/ml within a 4 week period.
- Have a near normal total cholesterol "a kind of fat in the body" lower than 240mg/dl and a LDL cholesterol "a kind of fat in the body" lower than 130mg/dl
- Have near normal results for tests that test the health of your kidney, pancreas, liver, blood and muscles.
- Have a negative serum pregnancy test and not be breast feeding prior to taking the study drugs

To Participate in the Study You Must Not

- Be actively using recreational drugs or alcohol, as this might affect your ability to participate in the study
- Have had a serious illness or opportunistic infections "illnesses that occur in people with a weakened immunity" that required hospitalization in the 30 days prior to study entry

- Have evidence of any cancer or opportunistic illness that will require treatment during the study period except some kinds of skin cancer
- Allergy to the study medication "atorvastatin" or any of its components
- Have had a history of myositis or rhabdomyolysis (diseases that result in muscle injury or swelling "inflammation") with use of any statins
- Have had a history of diseases of the muscle such as poly or dermatomyositis (these are diseases of the muscle which result in swelling or " inflammation" of the muscle)
- Be on any medication that do not mix "interact" with the study drug " atorvostatin" . Please see the attached listing If you are any of these medications please let your physician know.
- Use St.Johns wort as this can increase the amount of the study drug in your body
- Use grape fruit or grape fruit juice, as this can increase the levels of study drug in your body
- Be on any medication that might affect your immune response
- Have a low LDL cholesterol (a kind of fat in your body) that is less than 40 mg/dl
- Have had any vaccines within 6 weeks of entry into the study

Withdrawal From the Protocol

You may choose to withdraw from the protocol at any time. We may choose to withdraw you from the protocol at any time if we think it is not in your best interest to continue on the protocol, or if you fail to comply with the requirements of the protocol or if the DSMB, a panel of independent investigators who will review the data after we accrue 50 % of the patients, decides to stop the protocol. If the protocol is terminated for unanticipated reasons you will be withdrawn from the study. If you need to start antiretroviral therapy, you will be withdrawn from the study and referred to your primary physician. Any decision to start antiretroviral therapy will be done in consultation with your primary physician. If you need to start antiretroviral therapy you should do so after you have discontinued atorvastatin for one week. You may also be withdrawn from the study if blood tests that measure your liver functions are greater than 3 times the upper limit of normal on two successive measurements.

Duration of Study

The study will take 24 weeks to complete once you have been assigned to your group.

Risks/Discomforts/Monitoring

Risks

The possible risks and discomforts from being in this research study include risks from the study medication, from reductions in your cholesterol, those associated with phlebotomy (blood draw). Each one of these risks is explained in detail below:

Atorvastatin - The use of this drug in research studies (clinical trials) designed to win approval of this drug have demonstrated that about 2% of the population reported different side-effects such as chest pain, nausea, bronchitis (inflammation of the bronchus), rhinitis (similar to a runny nose), arthritis (swelling and inflammation of the joints), insomnia (difficulty sleeping) and dizziness, urinary tract infection and peripheral edema (swelling of your feet/leg). In addition this drug has been associated with increases in liver enzymes and rarely fatal liver failure. However, in most cases the liver enzymes come back to where they started (baseline) if the drug is stopped. This drug has also been associated with increases in muscle enzymes, muscle pain and a complication called rhabdomyolysis. This complication refers to a condition that is associated with injury to your muscles that can sometimes lead to kidney failure. There have also been some cases of altered behavior, memory loss and inflammation of the nerves (peripheral neuropathy) with the use of this drug.

While all risks to you cannot be foreseen, all attempts will be made to ensure your safety. This will include testing your blood, reviewing your symptoms and doing physical examinations at regular intervals as previously described. In addition a data safety monitoring board, which consists of a panel of individuals not associated with the study, will evaluate the data collected after half the subjects have been enrolled and completed the study. If this board feels that this trial should be discontinued because it poses a risk to the participants, the trial will be discontinued.

Pregnancy - Atorvastatin belongs to a class of drugs referred to as statins. This group of drugs cannot be used during pregnancy as it may cause damage to the unborn baby. To participate in this study you will be required to use two reliable methods of contraception at all times while you are on this study and will undergo periodic testing to confirm your pregnancy status. If you become pregnant while on study you will be asked to discontinue all on study medications. We will continue to follow you throughout the pregnancy and immediately after pregnancy to assess for adverse effects.

Hypocholesterolemia (low cholesterol) - As your cholesterol (a kind of lipid in your blood) will be normal at the beginning of the study we anticipate that your cholesterol will fall during this study because the drug being used is known to reduce cholesterol. Not much is known about what happens in humans when the cholesterol falls to a very low level. In animal studies when the cholesterol levels fall to very low levels, there are reports of damage to the brain and eyes. We will ensure that your cholesterol does not fall to such levels, by ensuring that a physician not associated with the study team, reviews your cholesterol. If he/she feels that your cholesterol is too low (that is levels that could be potentially harmful) he will discuss this with the study investigators and you will be withdrawn from the study. In addition all subjects will be followed for signs and symptoms and problems with your nervous system/ eyes.

Phlebotomy (sampling of blood by needle puncture) - The risks associated include bleeding, bruising, and fainting. To minimize risk, patients will have their blood taken in the sitting position and will be monitored for 10 minutes after the procedure.

Benefits

You will not benefit from taking part in this study, but the information we learn may help us with the management of HIV positive patients in the future. This includes the availability of a drug that is frequently used in the management of some of the complications of drugs currently used to control the virus and may have the potential to control the quantity of virus and affect the immune response in HIV positive patients.

Compensation

To compensate for your time and inconvenience of this protocol, you will be paid a total of $600.00 at the end of the study. If you choose to leave the study before the end, you will be paid according to the amount of time you participated, $50 for each visit you complete. The compensation will be provided as a lump sum at the end of your participation. If you need to stop the study because of toxicity, you will be paid the total amount.

Alternatives to Participation

This study provides no direct benefits to participants. You are in no way obligated to continue in the protocol even if you are eligible. The alternative to participation is not to enroll.

Additional Information

There will be no cost to you for study medications, clinic visits, examinations or laboratory and test procedures that are part of this study and that are obtained at the NIH. Medical costs of other treatment outside this study and outside of the NIH will not be the responsibility of the NIH. The NIH will provide only study-related medical care, and medical care and medications not directly related to the study must continue to be provided by your personal physician. We will be sending letters regarding your study participation and your care to your doctor routinely and as needed, and we will also use the fax and the phone to relay information to your doctor that he or she should know to best care for you. We will not ask your permission for each of these contacts. We will contact the physician you have named as your doctor, but you may give us a different physician to contact instead at any time. Once your participation in this study is completed, you will not be eligible for continuing care at NIH, unless you are eligible for another study at the NIH, but your doctors at NIH will be glad to provide telephone consultation to your own doctor on request. During the study, you will be told about any research that relates to your study, especially any findings from the study itself.

Genetic Testing

Some of the blood drawn from you as part of this study will be used for genetic tests. Genetic tests can help researchers study how health or illness is passed on to you by your parents or from you to your children. Some things to consider in thinking about whether or not to participate in these genetic studies include 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? There may be no treatment for certain conditions and this may cause some individuals to feel anxious, depressed, or stressed. Additional genetics counseling and advice is available from the National Institutes of Health 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.

Some of the blood drawn from you as part of this study may be used for a test for HLA type, which is a genetic test of markers of the immune system. It is usually used to match bone marrow or organ transplants. For research, HLA testing might be used to try to identify factors associated with the progression of HIV disease or related conditions. In addition, determining HLA type is necessary to be able to perform certain research studies. 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.

Genetic testing can also be used to determine if people are directly related. These tests can reveal that a person's biological parents are someone other than their legal parents. If these facts were not known previously they could be troubling to learn. It is our policy to not discuss such information unless it has direct medical or reproductive implications for you or your family. By agreeing to participate in this study, you do not waive any rights that you may have regarding access to and disclosure of your records. For further information on those rights, please contact Dr. Maldarelli, principal investigator. Any genetic information collected or discovered about you or your family will be confidential. Medical records containing this information will be kept under lock and key. We will not release any information about you or your family to relatives, any insurance company, or employer unless you sign a release requesting us to do so. Genetic information can be requested and obtained when a person applies for health insurance or a job and has signed a release.

Stored Samples and Future Research

Blood left over from this study will be stored. These stored samples will help us learn more about HIV, immune deficiency or related conditions. In general, the research tests we perform are not like routine medical tests, and may not relate directly to your medical care, so we may not put future test results in your medical record. However, if you wish, someone on the study team will discuss the test results with you. We will not share these test results with your private doctor unless you ask us to do so.

By agreeing to participate in this study, you do not waive any rights that you have regarding access to and disclosure of your records. For further information on those rights, please contact Dr. Maldarelli.

Labeling of Stored Samples

We will label your stored samples with a code that only the study team can link to you. We will keep any information that can be traced back to you private to the extent permitted by law.

Future Studies

Other investigators may want to study your stored samples. If so, the NIH study team may send your samples to them, along with a coded label. The study team may also share information such as your gender, age, health history, or ethnicity. In some cases, an Institutional Review Board (IRB) will review new research proposals that would like to use your samples. The IRB is a committee that oversees medical research studies to protect volunteers' rights and welfare.

Investigators will *only* use your samples for research. We will not sell them. Future research that uses your samples may lead to new products, but you will not receive payment for these products. Some future studies may need health information (such as smoking history or present health status) that we don't already have. If so, the NIH study team will contact you for this information.

Benefits

In general, future research that uses your samples will not help you, but it may help us learn what causes AIDS, immune deficiency, or related conditions. This research may also help us learn how to prevent or treat the condition.

Risks

The greatest risk 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.

Making Your Choice

If you agree to participate in this study, you agree to let us store your samples for future research. You also agree that we can contact you again in the future. No matter what you decide, you may still participate in other studies at NIH. However, your refusal to let us store your samples may lead to your withdrawal from this specific study. Even if you agree now to let us store your samples, you can change your mind later. If you do, please contact us and say that you do not want us to use your samples for future research.

As part of your participation in this study, it will be necessary to test your blood for the presence of antibodies to the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS). In order to perform the test, a small amount of blood (approximately 2 teaspoons) will be withdrawn from one of your arms with a needle. You may experience some slight discomfort at the needle entry site and there may be some bruising. In addition, there is a very small risk of you fainting or of infection at the needle entry site. If your test results are found to be positive, or if you are otherwise diagnosed as having AIDS, you should be aware of the following Clinical Center HIV Testing Policy:

1. Your physician will notify you promptly of the HIV test results.

2. Your physician and/or the Clinical Center HIV counselor will offer you, and any current and/or ongoing sexual partner(s) (spouses are generally considered to be current or ongoing sexual partners) or needle-sharing partner(s) you identify, information on the meaning of the test results and how to prevent the spread of the infection.

3. Because the virus may be transmitted in several ways, it is important that you inform sexual and/or needle-sharing partner(s) that any, or all, of them may have been exposed to the HIV virus and encourage them to be tested. If you request it, staff at the Clinical Center will assist you in notifying your partner(s) and arrange counseling for them through an HIV counselor.

4. The results of your HIV test and/or documentation of the diagnosis of AIDS will become a part of your Clinical Center medical record and, as such, will be protected from unauthorized disclosure by the Federal Privacy Act of 1974. In general, access to your medical record will be restricted to those health care professionals directly involved in your care or in the conduct of ongoing biomedical research, and information is not usually released to other third parties without your permission or that of your designated representative. However, there are some particular routine uses of such information of which you should be aware.

   a. If you are unwilling or unable to notify your partner(s), the Clinical Center is responsible for attempting to contact and inform them of their possible exposure to the virus. Reasonable attempts will be made to protect your identity including withholding your name when notifying any partner(s) of their possible exposure. Some notification or counseling of current and/or ongoing partners may be carried out through arrangements with, or referral to, local public health agencies.

   b. A summary of your care at the Clinical Center will be sent to the physician who referred you here for treatment.

   c. The Clinical Center may report certain communicable diseases, such as HIV infection, to appropriate State and Federal government agencies.

      i. For Clinical Center patients who are Maryland residents, the Clinical Center reports by "Patient Unique Identifier Number" (rather than by name) newly obtained HIV-positive results from its laboratory to the Maryland Department of Health and Mental Hygiene. Patient Unique Identifier Number is: last four digits of social security number, birth month, birth day, birth year, race and gender.

ii. For Clinical Center patients who are Maryland residents, the Clinical Center reports by name new cases of AIDS to the Maryland Department of Health and Mental Hygiene.

iii. For Clinical Center patients who are not Maryland residents, the Clinical Center reports HIV-positive results and/or AIDS to the patient's primary care/referring physician.

If you have any questions regarding the HIV testing or the information provided above, you are encouraged to discuss them with your physician and/or a Clinical Center HIV counselor: (301) 496-2381.

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 other authorized people.

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.

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, Frank Maldarelli, M.D., Building: 10, Room 12S245, Telephone: (301) 435-8019. Other investigators you may call are Rose McConnell (301) 443-5643.

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 _____

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 _____

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 _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM APRIL 14, 2008 THROUGH APRIL 13, 2009.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____