Why am I being asked to volunteer?

You are being invited to participate in a research study because you have HIV infection and are on HIV treatment. HIV infection can cause changes in a type of blood cell (“monocytes”) that are thought to lead to brain complications in some people with HIV infection. The research is designed to determine if a type of medication called Atorvastatin can reverse these changes in blood monocytes. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

Some people with HIV infection develop neurological (brain) problems, which eventually can interfere with normal thinking and brain function. One way that HIV affects brain function is by causing inflammation in the blood, causing changes in a type of white blood cell called monocytes. It is believed that when monocytes are affected by HIV in this way, they can eventually enter the brain and cause damage there.

Atorvastatin is a drug that is used commonly to treat high cholesterol and to prevent heart attacks or strokes. In addition to lowering cholesterol, it can also decrease inflammation. The goal of this study is to test whether Atorvastatin will decrease inflammation and reverse the changes in blood monocytes in people with HIV infection.
Eligibility to enroll in the study
You are eligible to participate in the study if you:

- have HIV infection and are on HIV medications presently and there have been no changes in the combination of HAART (highly active anti-retroviral therapy; a class of medications that are used to treat HIV) drugs used within 4 weeks of study entry.
- have plasma (a component of blood) viral load ≤200 copies/ml for at least 6 months at screening visit
- do not use recreational drugs, and do not drink more than one drink of alcohol per day
- are not allergic to atorvastatin or have had any prior reaction to atorvastatin (or other drugs in the “statin” group)
- do not have a history of muscle disease or liver disease, or have active hepatitis (liver inflammation) or serious kidney or blood disease.
- are not on any other lipid-lowering agents (ie, cholesterol-lowering agents) or any medications known to interact with atorvastatin, and do not use any over-the-counter, vitamin or herbal supplements that can interact with atorvastatin. It will be important that any new medications or over-the-counter supplements or vitamins are discussed with the study staff to be sure it is safe to take them with atorvastatin.
- If female: are not breast-feeding and, if able to become pregnant, are willing to use a method of contraception during the study period and undergo pregnancy testing on a monthly basis.
- are willing to participate in the study, come to study visits, have samples taken and have neuropsychological testing (these are tests that examine thinking skills) on 4 study visits.

How long will I be in the study? How many other people will be in the study?
You will participate in the study for a total of 38 weeks. During this time you will be on treatment with the Atorvastatin or placebo for a total of 24 weeks. The overall study will last for about 4 years and will include approximately 30 subjects.

What am I being asked to do?
In the first treatment period you will be asked to take the medication Atorvastatin or placebo for 12 weeks. If you are on HAART medications that include protease inhibitors (PI), you will be asked to take Atorvastatin or placebo at 10 mg/day for 2 weeks, then 20 mg/day. If you are on HAART medications that do not include PI or non-nucleoside reverse transcriptase inhibitors (NNRTIs), you will be asked to take Atorvastatin / placebo at 20 mg/day for 2 weeks, then 40 mg/day. If you are on NNRTI HAART medications, you will be asked to take Atorvastatin / placebo at 40 mg/day for 2 weeks, then 80 mg/day. There will then be a period of 6 weeks without study medication (“washout phase”), followed by a second treatment
period in which treatment will be switched and you will be asked to take placebo or Atorvastatin for 12 weeks, at the same dose as in the first treatment period.

Blood will be taken prior to beginning Atorvastatin / placebo, periodically while on treatment and during the washout phase for the duration of the study. The blood samples will be used to test whether the monocytes have changed, or whether there are changes in blood proteins that are made by monocytes when they are activated.

You will also be asked to undergo neuropsychological testing at 4 visits during the treatment period.

In addition, 16 subjects will be asked to undergo 2 lumbar (spine) punctures (at entry visit and week 12) to obtain a small amount of cerebrospinal fluid (this is the fluid that surrounds the brain) for study. No separate eligibility criteria are needed for lumbar puncture therefore individuals screened for the study will be asked whether they are willing to participate in the same if they screen pass.

☐ I agree to participate in the lumbar puncture sub-study ____________________________

☐ I will not participate in the lumbar puncture substudy

Tests when starting the study (2 weeks before beginning treatment)

- A medical history and physical examination. The history will include a review of all of your previous health problems, and your recent and current medications.
- Blood tests: If you have not had a blood count and blood chemistry within the past month, these tests will be done. Blood chemistry will include tests to monitor for liver or muscle problems at the start of the study (ALT/AST and CPK). We will also test for inflammation (high sensitivity C-reactive protein, or “hs-CRP”). Approximately 25 mL of blood (1-1/2 tablespoon) will be taken for these tests. An additional 10 mL blood (less than one tablespoon) will be collected and stored for later testing of plasma proteins.
- Blood will be drawn for HIV viral load testing and CD4 count if it has not been done within the past 3 months.
- Women will have a pregnancy test on a urine sample
- If you do not have evidence of any serious liver, muscle, kidney or other problems, and the blood test shows hs-CRP ≥ 2 mg/L, you will be asked to enroll in the treatment study.

1st treatment period

Tests when starting treatment with Atorvastatin / placebo

- Blood will be collected and used to examine the monocytes, and some will be stored for testing plasma proteins. In addition, blood will be drawn for HIV viral load testing. All together this will include approximately 100 ml (6-1/2 tablespoon) of blood.
In addition, neuropsychological testing will be done to detect any HIV-associated neurocognitive disorders.

If enrolled in the LP sub-study, an LP will be carried out to collect cerebrospinal fluid (CSF) to test for the presence of inflammation.

**Tests 2 weeks after starting Atorvastatin / placebo**

- Blood will be drawn for blood count and blood chemistry test, including tests to monitor for liver and muscle problems (ALT/AST and CPK). Additionally, some blood will be drawn for testing plasma proteins. All together this will include approximately 30 mL (2 tablespoons) of blood.

- Women will have a pregnancy test on a urine sample

- If the blood tests show no indication of problems, the dose of Atorvastatin will be increased (from 10 mg/day to 20 mg/day if you are on HAART that includes PI; from 20 mg/day to 40 mg/day if you are on HAART medications that do not include PI or NNRTI); from 40 mg/day to 80 mg/day if you are on HAART that include NNRTIs.

**Tests 6 weeks after starting Atorvastatin / placebo**

- Blood will be drawn for blood count and blood chemistry test, including tests to monitor for liver and muscle problems (ALT/AST and CPK). In addition, some blood will be collected to examine the monocytes and some will be stored for testing the plasma proteins. All together this will include approximately 90 mL (6 tablespoons) of blood.

- Women will have a pregnancy test on a urine sample

**Tests 12 weeks after starting Atorvastatin / placebo**

- Blood will be drawn for blood count and blood chemistry test, including tests to monitor for liver and muscle problems (ALT/AST and CPK). Blood will also be taken for monitoring HIV viral load, CD4 counts and lipid levels. In addition, blood will be taken for examining the monocytes and some will be stored for testing plasma proteins. Overall, approximately 120 mL (8 tablespoons) of blood will be taken.

- Women will have a pregnancy test on a urine sample

- In addition, neuropsychological testing will be done to detect any HIV-associated neurocognitive disorders.

- If enrolled in the sub-study, an LP will be carried out to collect CSF to test for the presence of inflammation.

**Tests during the washout phase (week 12 through week 18)**

- Blood will be drawn at week 16, for blood chemistry tests, including tests to monitor for liver and muscle problems (ALT/AST and CPK). In addition, some blood will be stored for testing plasma proteins. All together this will include approximately 20 mL (1-1/2 tablespoons) of blood.
- Women will have a pregnancy test on a urine sample

### 2nd treatment period

**Tests 18 weeks after entering the study (when starting the 2\textsuperscript{nd} treatment phase with placebo / Atorvastatin)**

- Blood will be drawn to test for hs-CRP, lipid levels, CD4 counts and viral load. Blood will also be collected and used to examine the monocytes, and some will be stored for testing plasma proteins. Approximately 110 mL of blood (7-1/2 tablespoons) will be taken at this visit.
- In addition, neuropsychological testing will be done to detect any HIV-associated neurocognitive disorders.

**Tests 20 weeks after entering the study (2 weeks after starting the 2\textsuperscript{nd} treatment phase with placebo / Atorvastatin)**

- Blood will be drawn to do blood chemistry tests to monitor for liver and muscle problems (ALT/AST and CPK). Blood will also be drawn for testing lipid levels and some will be stored for testing plasma proteins. All together this will include approximately 30 mL (2 tablespoons) of blood.
- Women will have a pregnancy test on a urine sample

**Tests 24 weeks after entering the study (6 weeks after starting the 2\textsuperscript{nd} treatment phase with placebo / Atorvastatin)**

- Blood will be drawn to do blood chemistry tests to monitor for liver and muscle problems (ALT/AST and CPK). In addition blood will also be collected and used to examine the monocytes, and some will be stored for testing plasma proteins. About 100 mL of blood (6-1/2 tablespoons) will be taken at this visit.
- Women will have a pregnancy test on a urine sample

**Tests 30 weeks after entering the study (12 weeks after starting the 2\textsuperscript{nd} treatment phase with placebo / Atorvastatin)**

- Blood will be drawn to do the same tests that were done in the week 12 visit. Approximately 120 mL of blood (8 tablespoons) will be taken at this visit.
- Women will have a pregnancy test on a urine sample
- In addition, neuropsychological testing will be done to detect any HIV-associated neurocognitive disorders.

**Tests at end of 2\textsuperscript{nd} washout phase (week 36 of the study)**
Blood will be collected and used to examine the monocytes, and some will be stored for testing plasma proteins. All together this will include approximately 70 mL (approximately 5 tablespoons) of blood.

**Explanation of tests**

**Monocyte testing** White blood cells will be analyzed in the laboratory by a method that determines if treatment has changed the types of proteins on the surface of the cells, and stored for later analysis of whether treatment has changed the types of proteins the monocytes makes based on RNA levels.

**Plasma protein testing** Monocytes release certain proteins into the liquid part of the blood (plasma). After the study is complete, we will test the stored plasma samples to determine if treatment has changed the amount of these proteins the monocytes released into the blood.

**Neuropsychological testing** This is a standard test that determines the ability and speed of a person’s thinking, memory and motor coordination. This test takes about a half hour, and is one by answering questions or working with a pegboard, with our study personnel.

**Lumbar Puncture** This is a procedure (sometimes called a spinal tap) to collect fluid from the spinal area, to test if the study treatment will decrease inflammation in the brain and nervous system. It is a test done routinely for the clinical diagnosis of brain or other neurological problems, but in this case will be done for research purposes. Your lower back will be cleaned using an antiseptic solution. Then, using a very small needle, an area of the back will be numbed using Lidocaine (novocaine). After the area of the back is numbed up, a needle will be introduced into the spinal canal, and about 10 ml (1/3 ounce) of fluid will be removed. The needle will be removed, and you will be asked to rest for several hours afterwards.

**What are the possible risks or discomforts?**

We will minimize the chance of any risk occurring by carefully questioning you for anything that might increase your chance of having a side effect from Atorvastatin, and by blood tests prior to beginning treatment and during treatment. The following risks may occur as the result of your participation in this research:

- **Atorvastatin treatment**

  The main side effects of Atorvastatin treatment are possible liver problems or muscle problems. The liver problems include changes in the liver blood tests, and will be monitored, and it would be very important to immediately report any change such as yellowing of the skin or eyes or dark urine. The muscle problems (“myopathy”) include muscle pain or damage to the muscles. A blood test for muscle injury will be monitored, and it would be very important to immediately report any new muscle pain or weakness or dark urine. In very rare cases these side effects may be severe.
Atorvastatin may cause fetal harm in pregnant women and may have serious adverse reactions in nursing infants. Therefore individuals (especially women), participating in the study must use a form of contraception to avoid pregnancy and must not be breastfeeding.

Some other side effects associated with taking Atorvastatin include allergic reactions or rash; fever or fatigue; abdominal pain.

- **Blood drawing**
  
  Bruising, bleeding, fainting and infections may result from obtaining blood.

- **Lumbar Puncture**
  
  The most common risk of a lumbar puncture is that it can cause a temporary headache. Lying down for a few hours after the test can make a headache less likely to occur. Other problems are rare and include infection or bleeding. Very rarely, some people can have an allergic reaction to Lidocaine used for numbing.

**What if new information becomes available about the study?**

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

**What are the possible benefits of the study?**

You are not expected to get any benefit from being in this research study. Your participation will help us learn whether Atorvastatin is a treatment that might be useful to help prevent or treat neurological (brain) complications of HIV infection.

**What other choices do I have if I do not participate?**

You do not have to participate in this research.

**Will I be paid for being in this study?**

The study involves one screening visit plus 10 study visits, for a total of 11 visits. You will be paid $50 for the screening visit. You will also be paid $50 for each study visit. If you are enrolled in the Lumbar puncture (LP) sub-study you will also be paid $200 for each LP. Therefore if you are not enrolled in the LP sub-study you will be paid a total of $550 and if you are enrolled in the LP sub-study, you will be paid a total of $950 for the entire study. Half of the amount for each study visit will be paid at the time of the visit, and the remaining half will be paid at the end of the entire study. Please note that if you receive more than $600 in payment in one year for participation in research studies at the University of Pennsylvania, you must provide an Individual Tax Identification Number or Social Security Number for tax purposes.
Will I have to pay for anything?

You and/or your health insurance will not be billed for any of the research procedures performed in this study.

What happens if I am injured from being in the study?

If you have a medical emergency during the study you should go to the nearest emergency room. You may contact the Principal Investigator or Emergency contact listed on page one of this form. You may also contact your own doctor, or seek treatment outside of the University of Pennsylvania. Be sure to tell the doctor or his/her staff that you are in a research study being conducted at the University of Pennsylvania, and the name of the medicine you are on. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

In the event that you are hurt or injured as a result of participation in this research study, please contact the investigator listed on page one of this form.

In the event of any physical injury resulting from research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise offered from the University of Pennsylvania. If you have an illness or injury during this research trial that is not directly related to your participation in this study, you and/or your insurance will be responsible for the cost of the medical care of that illness or injury.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the National Institutes of Health without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.

- You have not followed study instructions.

- The Sponsor, the study Principal Investigator, or the National Institutes of Health has decided to stop the study.

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your future care.

Who can see or use my information? How will my personal information be protected?

The researchers that are part of this study will take steps to prevent any misuse of your specimens and research information. They will also take steps to protect the confidentiality of your information. Your research records and specimens will be identified by a code to separate them from your personal information or your identity. The researchers involved with this study will make every reasonable effort to protect the confidentiality of your information.
Your information will be kept in locked cabinets or in secured computers and your specimens will be protected in a secure facility.

**Who will have access to my specimens, data and medical information?**

Your medical and research records may be reviewed by The University of Pennsylvania, a research ethics committee (Institutional Review Board or IRB), the NIH, the Office for Human Research Protections, and the research staff. The purpose of such review would be to be sure the study is carried out safely and correctly.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR (Electronic Medical Record) maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Results of research procedures performed as part of your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

Please refer to the separate "HIPAA Privacy Authorization" document that explains more specifically how your personal information will be protected.

In addition, a description of this clinical trial will be available on [http://www.clinicaltrials.gov](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.

**Who can I call with questions, complaints or if I’m concerned about my rights as a research subject?**

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.
When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

________________________               ____________________________________
Name of Subject (Please Print)                 Signature of Subject   Date

________________________    ____________________________________
Name of Person Obtaining Consent (Please Print)  Signature                                      Date