Partners HealthCare System
Research Consent Form

Subject Identification

General Template - Drug Clinical Trial
Version Date: January 2010

Protocol Title: Atazanavir and Endothelial Function in Older HIV Patients

Principal Investigator: Joshua A. Beckman, MD

Site Principal Investigator:

Description of Subject Population: HIV-infected adults receiving suppressive ART consisting of co-formulated tenofovir/emtricitabine plus a non-atazanavir/ritonavir third agent: Aim 1

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

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 Website will include a summary of the results. You can search this Web site at anytime.

Why is this research study being done?

With an estimated 33.2 million people in the world infected with the virus, HIV is a major medical problem. With medical treatment, people with HIV now survive a much longer period of time. However, it has become clear that people with HIV are at a higher risk of having a heart

attack compared to people without HIV. We would like to find out if certain HIV medications may reduce the risk of heart attack better than others.

The purpose of this study is to see if switching to atazanavir will improve blood vessel function. Studying blood vessel function is a method that investigators use to understand if a treatment may reduce the chances of a heart attack.

We would also like to find out if atazanavir improves the ability of cells in your body to use blood sugar for energy and reduce inflammation (a response of body tissues to injury or irritation), and free radicals. Free radicals are responsible for aging, tissue damage, and possibly some diseases. At high levels, free radicals can cause cell damage. Each of these items has been linked to poor blood vessel function and a higher risk of heart attack. We will study blood vessel function and the other items that may disturb it. We will compare subjects taking atazanavir and ritonavir to subjects taking a non-atazanavir based therapy.

Atazanavir is approved by the U.S. Food and Drug Administration (FDA) to treat HIV.

Ritonavir is approved by the U.S. Food and Drug Administrate (FDA) to treat HIV.

We are asking you to take part in this research study because you are infected with HIV and are clinically-stable. You are currently receiving a combination pill tenofovir/emtricitabine. You are also receiving a FDA-approved protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or raltegravir. Examples of a PI are indinavir and fosamprenavir. Examples of a NNRTI are efavirenz, nevirapine, and delavirdine.

About 60 subjects will take part in this research study at Brigham and Women's Hospital (BWH).

Bristol-Myers Squibb is paying for this research to be done.

How long will I take part in this research study?

It will take you approximately 6 weeks to complete this research study. During this time, we will ask you to make 4 study visits to BWH.

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.

Visit 1 (Screening):

This visit will take about 1 hour and 15 minutes. During this visit, we will do some tests and procedures to see if you qualify to take part in this research study. The study doctor will review the results of these tests and procedures. If you don't qualify, the study doctor will tell you why.

At this visit, we will:

- Ask about your medical history, including any illnesses or health problems, your history of HIV-1 disease-related events, and medications you have taken within the last 3 months.
- Give you a complete physical examination, including measuring your height, weight, and blood pressure.
- Perform an ECG
- Test your blood for:
  - Routine tests
  - Tests related to your HIV, such as chemistry, complete blood count, CD4+(white blood cell that fights infection) cell count, and to measure the amount of HIV-1 in your blood
  - Pregnancy, if you are a woman able to become pregnant. Pregnant women cannot take part in this study.
  - Confirmation that you are post-menopausal (unable to get pregnant), if you are a post-menopausal female.

For your Safety During the Study
For your safety during the study, call the study doctor BEFORE you take any medications or health supplements.

Baseline Visit (Day 1/Visit 2):

We will ask you to come back to the study center within 2 weeks after the Screening Visit for the Baseline Visit. This visit will last about 1 hour and 30 minutes. We will ask you to come in

after fasting for at least 8 hours. Fasting means that you cannot eat or drink anything except for water and taking your medications for at least 8 hours before the visit. If you do not fast before the visit, we will ask you to return to the study center within 72 hours after fasting for at least 8 hours.

During this visit, we will:

- Perform an ultrasound test to see how the brachial artery (in your arm near the elbow) responds to certain tests. Ultrasound takes pictures by bouncing sound waves off tissues and organs in your body. During the testing, we will ask you to lie quietly on your back on a portable bed. The lights in the room will be dimmed.

  We will put a cool gel on your arm. An ultrasound probe (device that looks like a microphone) will be moved back and forth over your arteries. Computer pictures of your arteries will be taken before and after inflating a blood pressure cuff for 5 minutes on the upper part of the arm. We will measure the response of your artery(ies) to this temporary "blockage" of blood flow (inflating the blood pressure cuff). If you are unable to tolerate the blood pressure cuff, you may ask that it be removed and we will stop the study.

  Next, we will give you a small dose of nitroglycerin, a medicine that causes blood vessels to dilate (expand). Nitroglycerin is approved by the FDA to treat angina (chest pain). The tablet is placed under your tongue. We will take ultrasound pictures of your arteries again to see the effect of the nitroglycerin. The ultrasound takes about one hour. We will check your blood pressure and heart rate during the ultrasound.

- Ask you for a urine sample to test for pregnancy, if you are a female who is able to become pregnant.

- Draw blood samples for complete blood count and sugar levels.

- Counsel you regarding the importance of taking all of your medications and study drug as directed.

If you still qualify for the study, we will assign you by chance (like a coin toss) to one of the following study groups:

- Study Arm 1: You will continue the HIV medication you are currently taking.
- Study Arm 2: You will continue to take tenofovir/emtricitabine. You will stop taking the third HIV medication you are currently taking and will begin taking atazanavir (300 mg) and ritonavir (100 mg) for 28 days.

You and the study doctor cannot choose your study group. You will have an equal chance of being assigned to each group.

Taking the Study Drug

If you are in Study Arm 2, we will give you a supply of study drug (atazanavir and ritonavir) to take home with you.

You will take the study drug by mouth, once a day for 28 days. The study drug must be taken with food. It is important for you to follow our instructions about how to take the study drug. Bring any unused study drug with you to the last study visit.

If you are in Study Arm 1, you will continue to take your current medication as directed.

Your Study Drug Diary

We will give you a study diary to fill out at home each day. You will write down the time you take the study drug, how much study drug you take, and whether you have any side effects. Bring this diary with you to each study visit, so we can track your progress.

Visit 3 (Day 7):

Visit 3 will take about 1 hour and 30 minutes. At this visit, we will:

- Perform a physical exam, including height, weight, and blood pressure
- Draw a blood sample
- Perform an ECG
- Ask you about side effects or health problems since your last visit

- Review your drug diary
- Perform a ultrasound test

Visit 4 (Day 28)

Visit 4 will take about 1 hour and 30 minutes. At this visit, we will:

- Perform a physical exam, including height, weight, and blood pressure.
- Draw a blood sample
- Ask you about side effects or health problems since your last visit
- Collect any unused study drug
- Review your drug diary
- Perform a ultrasound test

We will draw a total of about 22 tablespoons of blood during the entire course of this research study.

After You Complete the Study

After you complete the study, we will refer you back to your own doctor for your ongoing medical care.

Stopping the Study Early

If you decide to stop taking part in the study for any reason, we will ask you to make a final study visit. You will need to return all unused study drug and your study diary at this visit. The final study visit will take about 30 minutes. At this visit, we will:

- Give you a physical exam
- Ask about any side effects or health problems since your last visit
- Draw a blood sample
- Collect any unused study drug
- Collect your drug diary

Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study doctor thinks it is best for you to stop taking the study drug
- You can't make the required study visits
- The Sponsor decides to stop the study
- We stop doing the study for other reasons

If this happens, the study doctor will explain why you need to stop taking part in the study. We will ask you to come in for a final study visit as described above.

STORAGE OF BLOOD SAMPLES

A portion of your blood sample drawn at each visit will be frozen and stored at Brigham and Women's Hospital. The stored blood will be used to study blood sugar use, inflammation, and free radicals at the end of the study. These stored blood samples may also be used by the Sponsor or its research partners to understand factors that may affect blood vessel function, like new tests for inflammation or free radicals that aren't currently known.

We will label all your samples with a study code instead of your name. The key to the code connects your name to your health information and samples. The study doctor will keep the key to the code in a password protected computer or locked file. Only study staff personnel at Brigham and Women's Hospital and representatives of Bristol Myers, Inc. will have access to your stored samples.

If at any time you choose to stop taking part in the study and want to have your samples destroyed, contact the study doctor.

Bristol-Myers Squibb may use health information that identifies you to do the research described in this form, and to do related research. This means research related to Atazanavi**r** alone, or in combination with other drugs/devices.

Bristol-Myers Squibb may use study information that no longer identifies you to do ANY type of research.

What are the risks and possible discomforts from being in this research study?

Risks of Taking Atazanavir

The possible side effects of Atazanavir are:

- nausea
- jaundice (yellowing of the skin)
- rash
- headache
- abdominal (belly) pain
- vomiting
- sleeping difficulties
- dizziness
- muscle pain
- loss of sensation
- diarrhea
- depression
- fever

Risks of Taking Ritonavir

The possible side effects of Ritonavir are:

- feeling weak/tired
- nausea
- vomiting
- diarrhea
- loss of appetite
- abdominal pain
- changes in taste
- tingling feeling or numbness in hands or feet or around the lips
- headache
- dizziness

There may be other risks of Atazanavir or Ritonavir that are currently unknown.

Allergic Reaction Risks

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, sweating, a fast pulse (heart beat), or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.

Risks of Ultrasound

During the ultrasound test, we will inflate a blood pressure cuff on your upper arm to a high pressure for 5 minutes. This may cause discomfort or aching. The ultrasound test should not cause you any discomfort.

Risks of Nitroglycerin

We will give you a small dose of nitroglycerin to take (under the tongue) during the ultrasound testing. Nitroglycerin may cause a temporary headache. Less than 1 in 100 people may develop low blood pressure or a vasovagal reaction (fall in heart rate with low blood pressure). Your blood pressure and heart rate will be checked many times throughout the study and a study doctor will be present during the testing. If the top number of your blood pressure at rest is lower than 100 mm Hg, we will not give you nitroglycerin.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant

The effect of Atazanavir and Ritonavir on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding

If you are a menopausal woman and have not had a period for the past 12 months or more, you will not need to have a pregnancy test. Also, you will not need to have a pregnancy test if you

have had a hysterectomy (surgical removal of your uterus and/or ovaries). All other female subjects must have a negative pregnancy test before starting the study drug.

If you are sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below. You must use birth control for the entire study.

Acceptable birth control methods for use in this study are:

- Not having vaginal sex (abstinence)
- Surgical sterilization (hysterectomy or bilateral oophorectomy [removal of both ovaries])
- Limiting sexual activity to a male partner who has had a vasectomy (surgical procedure used to make a man sterile)
- Using two of the following forms of birth control listed below. At least one form of birth control must be a barrier method (condom or diaphragm):
    - Taking hormonal birth control pills orally and using condoms
    - Having hormonal birth control shots or patches such as Depo-Provera and using a diaphragm
    - Use of an intrauterine device (IUD) and condom
    - Double-barrier methods (condom and/or diaphragm without spermicide)

Hormone-based contraceptives (birth control pills, patches, injections, vaginal ring, or implants) may not be effective at preventing pregnancy when they are used with tenofovir/emtricitabine, atazanavir and ritonavir.

Even if you use highly effective birth control methods, you could still become pregnant. There is a slight chance that a pregnancy test could be wrong. If the pregnancy test is wrong and you receive the study drug while pregnant, the study drug may harm an unborn baby.

If you are female and miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking part in the study. The study doctor may ask for your permission to collect information about the outcome of your pregnancy and the condition of your newborn.

Males:
If you are a male who is able to father a child, you must use 2 effective methods of birth control during the entire study. One of the effective methods of contraception for use in this study must

be an effective barrier method. An effective barrier method includes a condom or diaphragm used without spermicide (a foam, cream, or gel that kills sperm). The other birth control method may include:

- being non-heterosexually active
- practice sexual abstinence
- be vasectomized

CONDOM USE

It has been proven that condom use decreases the risk of spreading HIV between sexually active individuals. To decrease your risk of transmitting the virus to another individual and to decrease the risk of being infected with a different strain of HIV, we recommend that condoms be used. Condoms should be used for all sexual activity including oral, vaginal, and anal sexual contact. Condom use is recommended in addition to your current form of birth control.

Risks of Taking Atazanavir and Ritonavir with Other Medications

If you decide to be in this study, there are some over-the-counter medications that you will not be able to take or will not be able to take at the same time as Atazanavir with Ritonavir. The study doctor will discuss the medications that you cannot take during the study. These medications could make the study drug not work as well or they could combine with the study drug and cause side effects. Not being able to take these medications may make the symptoms that you would normally take these medications for (like heartburn) worse or harder to treat. You should talk to the study doctor about all of the medications you are taking. Examples of medications that interact with Atazanavir and Ritonavir are Alfuzosin, Rifampin, Irinotecan, Triazolam, Midazolam, Ergot derivatives, Cisapride, St. John's Wort, Lovastatin, Simvastatin, Pimozide, Sildenafil, and Indinavir.

For your safety during this study, call your study doctor BEFORE you take any:

- new medications prescribed by your own doctor
- other medications sold over-the-counter without a prescription
- dietary or herbal supplements

Risks of Blood Draws

You may have a bruise (a black and blue mark) or pain where we take the blood samples. There is also a small risk of infection, lightheadedness, and/or fainting.

Other

Viruses that are resistant to the study drugs may develop while you are receiving the study drug. This may reduce your treatment options in the future. During the study, your study doctor will monitor (check) your HIV-1 levels for viral rebound (increase in HIV-1 levels after having earlier results of lowered HIV-1 levels). Resistant mutations develop most rapidly in people who do not take all of their HIV-1 drugs. Resistant mutations occur in viruses and make them able to resist treatment with a particular drug. Therefore, it is important to take all your study drugs as prescribed by your study doctor.

You may have a side effect that requires your study doctor to stop you from taking part in the study. You should contact your study doctor immediately if you feel that you cannot tolerate your drug regimen.

What are the possible benefits from being in this research study?

You will not benefit from taking part in this research study. Taking Atazanavir and Ritonavir is not expected to cure you of HIV. If you receive Atazanavir and Ritonavir, it is possible that your HIV-infection may improve while you are taking them.

Others with HIV may benefit in the future from what we learn in this study**.**

What other treatments or procedures are available for my condition?

You do not have to take part in this research study to be treated for HIV infection. Other treatments or procedures that are available to treat HIV infection include:

- Other available treatments for your disease include Ritonavir with Darunavir, Raltegravir, Sustiva, Kaletra, Epzicom and Truvada.

Can I still get medical care within Partners if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Your doctor can prescribe Atazanavir and Ritonavir for you even if you do not take part in this study.

Will I be paid to take part in this research study?

We will pay you $300 if you complete the study. You will not be paid for completing the Screening Visit (Visit 1). We will pay you $100 for completing the Baseline Visit (Visit 2), $100 for completing the Day 7 Visit (Visit 3), and $100 for completing the Day 28 Visit (Visit 4).

We will pay for your parking in the hospital garage during study visits.

We will pay for the cost of your transportation up to $10 per visit.

We may use your samples and information to develop a new product or medical test to be sold. The Sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

What will I have to pay for if I take part in this research study?

If you are assigned to Study Arm 2, Bristol-Myers Squibb will provide the study drugs (Atazanavir and Ritonavir) at no cost.

Study funds will pay for study visits, ultrasound, nitroglycerin, and all the tests and procedures that are done only for research.

Study funds will not pay for your combination pill tenofovir/emtricitabine. You will have to pay for it in the same way you did before you took part in this study.

Study funds will pay for certain study-related items and services. However, we may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care.

If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs.

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, 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. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Joshua Beckman, MD is the person in charge of this research study. You can call Dr. Beckman at 617-732-6320 from 8:30 AM till 4 PM. Dr. Beckman can be reached 24-hours a day, 7 days a week by calling the page operator at 617-732-6660 and asking for beeper # 17188. You can also call Paul Sax, MD at 617-732-8881 from 9 AM till 5 PM. Dr. Sax can be reached 24-hours a day/7 days a week by calling the page operator at 617-732-6660 and asking for beeper # 11943.

If you have questions about the scheduling of appointments or study visits, call our research assistants at 617-732-6320.

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 617-424-4100.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

During this research, identifiable information about your health will be collected. In the rest of this section, we refer to this information simply as "health information." In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so.

In this study, we may collect health information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable health information and why they may need to do so:

- Partners research staff involved in this study
- The sponsor(s) of this study, and the people or groups it hires to help perform this research
- Other researchers and medical centers that are part of this study and their ethics boards
- A group that oversees the data (study information) and safety of this research
- Non-research staff within Partners who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- The Partners ethics board that oversees the research and the Partners research quality improvement programs.
- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)

- Other:

Some people or groups who get your health information might not have to follow the same privacy rules that we follow. We share your health information only when we must, and we ask anyone who receives it from us to protect your privacy. However, once your information is shared outside Partners, we cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information.

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifying information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others.

You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent | Date/Time

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject | Date/Time

Consent of Non-English Speaking Subjects Using the "Short Form" in the Subject's Spoken Language

Statement of Hospital Medical Interpreter

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Hospital Medical Interpreter Date/Time

OR

Statement of Other Individual (Non-Interpreter)

As someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

Name Date/Time

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