

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

A5262, Version 1.0, 12/11/08: A Pilot Efficacy and Safety Trial of Raltegravir Plus
Darunavir/Ritonavir for Treatment-Naive HIV-1-Infected Subjects
CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

If you are seen at the Hospital of the University of Pennsylvania [HUP], your contacts are:

Principal Investigator:	Pablo Tebas, MD	(215) 349-8092
Coordinator:	Joseph Quinn, RN	(215) 349-8092
Study Nurse:	Larisa Zifchak, RN	(215) 349-8092
	Kathryn Maffei, RN	(215) 349-8092
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	Aleshia Thomas, RN	(215) 349-8092

24 Hour Emergency Number (215) 662-6059 Ask for the Immunodeficiency Program Doctor on call

Introduction:

You are being asked to take part in this research study because you are infected with the human immunodeficiency virus HIV, the virus that causes AIDS, and have never received treatment for your HIV. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is Pablo Tebas, MD. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

Financial Disclosure

The person leading this study received extra money from Merck & Co., Inc and Tibotec Pharmaceuticals for work that is not a part of this study. These activities may include consulting, advisory boards, giving speeches or writing reports.

Why Is This Study Being Done?

The main purpose of this study is to evaluate how well a new combination of study drugs (raltegravir plus darunavir/ritonavir) will lower the HIV viral load to undetectable levels in the blood of previously untreated patients. Patients who have certain kinds of transmitted resistance will also be included in this study because the study drug combination is likely to be effective for them as well.

There are now several recommended treatment regimens for a person with HIV infection who has not yet been treated. Most people who receive treatment and take their medications have a good result, which is usually determined by measuring the amount of HIV in the blood (viral load). The best response is when HIV becomes undetectable (less than 50 copies/mL) in the blood. However, not all people have a good response. About 25% (one out of four) of people do not reach an undetectable viral load, or have some side effect. A side effect can occur early after starting treatment or after a longer time on treatment.

Sometimes people become infected with an HIV virus that is already resistant to some of the standard treatments. This is called transmitted drug resistance. These people may not respond as well to standard HIV treatments. Transmitted HIV resistance is now an important problem in many parts of the United States. Your healthcare provider can test for resistant virus and this test (resistance test) is now recommended for all people before they start HIV treatment.

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Unfortunately, some of these resistant strains are in such small quantities (minority variants) that they are not picked up by standard resistance tests. It is possible for even very careful doctors or caregivers to miss a resistant virus that may make treatment with the usual recommended treatment less likely to get the viral load to undetectable levels. Side effects and transmitted resistant HIV are some of the reasons why research is needed to identify new HIV treatment regimens that are safe and active, even in people with transmitted drug resistance.

The study will also look at the safety and tolerability of this study drug combination, how well patients are able to take the study drugs on schedule, and how well their immune systems respond to the study drugs. The study will also look at how patients who have a transmitted drug-resistant virus respond to the study drugs. The blood levels of the study drugs and drug resistance will be evaluated in patients who do not respond to the study drugs.

The drugs used in this study are raltegravir (RAL) and darunavir (DRV)/ritonavir (RTV). RAL is the first integrase inhibitor (a type of anti-HIV drug) approved by the Food and Drug Administration (FDA) for treating people infected with virus that is resistant to many of the currently approved anti-HIV drugs. In this study, RAL will be used "off label" meaning that it will be used to treat persons who have never received treatment for HIV. This usage is not approved by the FDA. DRV, which must be given with RTV to make sure the blood levels are high enough to be effective, is a protease inhibitor (a type of anti-HIV drug) that is approved by the FDA for treating people with HIV infection.

The combination of DRV/RTV and RAL alone has not been studied in previously untreated people. Therefore, this is an exploratory study. However, each drug has been shown to be safe and effective when combined with other drugs in previously untreated people, and DRV/RTV (at the dose used in this study) is FDA approved for this patient population. Further, the combination of DRV/RTV and RAL plus other HIV medications is effective in most people with resistant virus. Studies in these patients have shown that enough of each drug reaches the blood when both drugs are given together. However, we do not have information about what the blood level of each drug will be, given that the dose of DRV/RTV in this study is different than the dose used in the people with resistant virus. Also, since RTV is used to increase the level of DRV in this study, only DRV and RAL are considered active drugs. Usually HIV-infected people are treated with three active drugs, so this is another reason why the combination of drugs used in this study is experimental.

How Many People Will Take Part in This Study?

About 111 people will take part in this study. About 10 people are expected to participate at the University of Pennsylvania.

How Long Will I Be in This Study?

You will be in this study about 52 weeks (about 1 year).

What Do I Have To Do If I Am In This Study?

If you agree to join this study, you will be asked to sign this consent form. After you have signed the form, you will be asked some questions and will undergo some tests at the screening visit to see if it is safe for you to join the study. The screening visit will take about 30-60 minutes.

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Screening

- You will have a clinical assessment that will include questions about your health and any medicines you have taken in the last 30 days.
- You will have about 3 tablespoons of blood drawn for routine blood tests, and possibly an HIV viral load and hepatitis B test (hepatitis B is a virus that can affect your liver).
- Resistance testing (a test to see if the virus in your blood is likely to respond to study drugs) results must be available before entering the study. This test will be done at the screening visit only if your healthcare provider has not already done it as part of your routine care.
- An HIV test may be required to document your HIV status.
- You will be asked to give a urine specimen.

If You Do Not Enroll Into the Study

If you decide not to take part in this study 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 your age, gender, race), clinical (for example your disease condition, diagnosis), and laboratory (for example your viral load and resistance test) information is being collected from you so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

Pre-Entry

You will come to the clinic for pre-entry evaluations. Pre-entry and screening evaluations may be done on the same day if you have records that an HIV viral load was done in the 90 days before study entry. The pre-entry visit will last about 30 minutes.

- You will have about 1 tablespoon of blood drawn for routine blood tests, an HIV viral load, CD4 and CD8 cell count (the number of white blood cells that fight infection).
- Blood (about 2 tablespoons) will be stored indefinitely for future immunology and virology tests.

Entry

If you have met all the requirements to enter the study, you will come to the clinic at least 24 hours after your pre-entry visit, but within 45 days of your screening visit, for entry evaluations. This visit will last about 30-60 minutes.

- You will be asked about any medicine changes you have had since screening.
- You will have a physical exam between screening and entry. The clinic staff will check your height and weight, and vital signs such as temperature, blood pressure, and pulse.
- You will have about 4 tablespoons of blood drawn for routine blood tests, HIV viral load, and CD4 and CD8 cell count. Lipid tests (blood fats and cholesterol) will be done, so you must not have anything to eat or drink, except water and required prescription medications, for at least 8 hours before coming to the clinic.
- Blood (about 1 tablespoon) will be drawn and stored indefinitely for future immunology tests.

The study drugs RAL and DRV will be given to you at this visit. You will take RAL twice a day by mouth. You will take DRV with RTV once a day by mouth with food. It is important that DRV and RTV be taken at the same time. The RTV is not provided by the study. You will have to get RTV through your healthcare provider.

After Entry

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After you start taking the study drugs, you will be asked to come to the clinic on Day 7 and at Weeks 4, 12, 24, 36, 48, and 52. At most visits, a brief physical exam will be done and your blood will be collected for routine blood tests, HIV viral load, and CD4 and CD8 cell count. At Weeks 24 and 48, you will have blood drawn for lipid tests, so you must not have anything to eat or drink, except water and required prescription medications, for at least 8 hours before coming to the clinic at those visits. At Day 7, and Weeks 4, 12, 24, and 48, blood will be drawn and stored to measure the amount of RAL and DRV/RTV in your blood, and you will complete a questionnaire about how you are taking your study drugs. For these visits, you will be instructed not to take your morning doses of DRV/RTV (if usually taken in the morning) and RAL. The questionnaire will take about 5 minutes to complete. At Weeks 12, 24, and 48, blood will be stored indefinitely for future immunology and virology tests. You will have about 1-3 tablespoons of blood drawn at most visits. At week 24 and 48, you will have about 5 tablespoons of blood drawn. Most visits will last about 30-60 minutes.

At Weeks 24 and 48, you will be asked to give a urine specimen to monitor for possible effects of the study drugs on your kidney function. At all visits until the end of the study, you will be asked about changes to any other medicines that you may be taking. You will receive study drugs and be followed to the Week 52 visit.

If at any point during the study your viral load increases to a certain level, you will be asked to come back in for some additional tests within 7 to 35 days. You will also have another viral load test to make sure the first one was correct. This visit will last about 30-60 minutes.

- You will be asked about any medicine changes you have had since your last visit.
- You will have a brief physical exam. The clinic staff will check your weight and vital signs such as temperature, blood pressure, and pulse.
- You will have about 2 tablespoons of blood drawn for routine blood tests, HIV viral load, CD4 and CD8 cell count, and resistance testing.
- Blood (about 2 tablespoons) will be drawn and stored indefinitely for future virology, immunology, and study drug level tests.
- You will be asked to complete a questionnaire about how well you are remembering to take your study drugs.

Early study drug or study discontinuation

If you stop taking the study drugs before the end of the study, you will be asked to return to the clinic for an additional visit. You will be asked to continue to be part of the study and attend study visits and complete evaluations for the duration of the study. After this additional visit, you will no longer have to have blood drawn for study drug levels and you will not need to complete the questionnaire.

If you are taken off study early or decide to leave the study early, you will be asked to return to the clinic for a final visit.

This visit will last about 30-60 minutes. You will have a brief physical exam, and have blood drawn (about 3 tablespoons) for routine tests, HIV viral load, CD4 and CD8 cell count, and future virology and study drug level tests. You will be asked to give a urine specimen. You will be asked to complete the questionnaire.

Other

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You will be told the results of HIV viral load tests, CD4 and CD8 cell counts, pregnancy tests, and routine blood tests done on this study.

Some of your blood will be stored (with usual steps taken to protect your confidentiality) and used for immunology, virology, and study drug level testing that is required for this study.

Some of your blood that is leftover after all required study testing is done may be stored (with usual steps taken to protect your confidentiality) and used for ACTG-approved HIV-related research. These samples may be held for an indefinite length of time. Storage of leftover blood is not a requirement to participate in the study and you may withdraw your approval for the storage of your leftover blood at any time. We cannot ensure that you will be told of the results of the research done on these samples. Please indicate with your initials below whether you agree to have your leftover blood samples stored.

_____ YES

_____ NO

Why Would The Doctor Take Me Off This Study Early?

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

- The study is cancelled by the ACTG, FDA, NIH, Office for Human Research Protections (OHRP), one of the drug companies supporting this study, or the University of Pennsylvania's Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants.)
- A safety monitoring committee recommends that the study be stopped early.

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

- Continuing the study drugs may be harmful to you.
- You need a treatment that you may not take while on the study.
- You become pregnant or are breast-feeding.
- You are not able to attend the study visits as required by the study

If I have to permanently stop taking study-provided drugs, or once I leave the study, how would drugs be provided?

During the study:

If you must permanently stop taking study-provided drug before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:

After you have completed your study participation, the study will not be able to continue to provide you with drug you received on the study. If continuing to take these or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

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What Are The Risks Of The Study?

The drugs 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 these drugs. 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.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking (including nutritional supplements and herbal medications) 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.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.

The use of potent anti-HIV drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Risks with Use of Raltegravir (RAL, Isentress)

The following side effects have been associated with the use of RAL:

- Diarrhea
- Nausea
- Headache
- Fever
- Vomiting
- Dizziness
- Abdominal pain
- Feeling weak
- Tiredness

In addition to the side effects listed above, additional serious reactions include:

- Allergic reaction
- Low amounts of red blood cells (anemia)
- Low amounts of white blood cells (neutropenia)
- Heart attack
- Irritation of the stomach lining (gastritis)
- Liver problems (hepatitis)
- Herpes
- Kidney problems, including kidney failure
- Rash, which may be severe

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Abnormal blood tests which have been seen in studies of RAL in combination with other HIV drugs include:

- Elevated liver related function tests, which may be a sign of liver problems
- Increase in an enzyme that may be a sign of pancreas problems (pancreatic amylase)
- Increase in an enzyme released by muscle cells, with or without symptoms such as muscle aches or pain, tenderness or weakness

Cancers have been seen in people who took raltegravir with other HIV drugs. The types of cancers seen are typical for people with very sick immune systems. It is unknown if the cancers were related to raltegravir use.

Protease Inhibitors (DRV and RTV are this type of anti-HIV drug)

The use of protease inhibitors may be associated with the following:

- Increases in the amount of triglycerides and/or cholesterol in the blood
- Development of diabetes or the worsening of high blood sugar

There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes.

Darunavir (DRV/RTV, PREZISTA/RTV)

The following side effects are also associated with the use of DRV given together with RTV:

- People taking DRV together with RTV may develop severe liver problems, which may be life-threatening. People who have increased liver function tests before starting DRV and people with liver diseases such as hepatitis B or C have an increased risk for worsening of their liver disease.
- Rash which, in some people, may be severe or life-threatening. Contact your healthcare provider if you develop a rash.
- Diarrhea
- Nausea
- Stomach discomfort
- Vomiting
- Headache
- Abnormal increases in cholesterol in the blood
- Abnormal liver function blood tests
- Abnormal pancreatic blood test

Note: Before starting DRV, you should inform your healthcare provider if you are allergic to sulfa medicines. Your healthcare provider can provide more complete information about the side effects of RTV (the medicine you need to take together with DRV).

Risks of Drawing Blood

Taking blood may cause discomfort, bleeding, and bruising where the blood is drawn. Occasionally, there is swelling in the area where the needle enters the body and there is a small risk of infection. There is also a risk of lightheadedness, fainting, and blood clots.

Are There Risks Related To Pregnancy?

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It is not known whether the drug or drug combinations in this study harm unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make someone else pregnant. Because of the risk involved, you and your partner must use at least one method of birth control. You must continue to use birth control until 60 days after stopping your medicines. You must choose one of the birth control methods listed below:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- IUD
- Hormone-based contraception

If you can become pregnant, you must have a pregnancy test before you enter this study and before you begin study medications (1 teaspoon of blood or a urine specimen will be collected). You will be told the results of the test. The test must show that you are not pregnant.

Breast-feeding

It is unknown whether the study drugs pass through the breast-milk and may cause harm to your infant. You must not breast-feed if you are in this study.

What If I Become Pregnant During This Study?

If you become pregnant or think you may be pregnant at any time during the study, tell your study staff right away. You will be asked to come in for a clinical assessment and have blood drawn (about 1 tablespoon) for a pregnancy test, other routine tests, and an HIV viral load. The study staff will talk to you about your choices and refer you to a provider of prenatal care if you do not have one. You will be told to stop taking the study medications, and you will be asked to continue to be part of the study and attend study visits and complete evaluations for the duration of the study. (You will not need to have blood draws for drug levels or storage of immunology and virology specimens, and will not need to complete the questionnaire.)

You and your physician will decide what anti-HIV drug combination would be best for you to continue. These medications will not be provided by the study. This study will not provide care related to your pregnancy, the delivery of your baby, or the care of your baby. You must arrange for your care and your baby's care outside of this study. This study will not provide your baby any anti-HIV drugs. Long-term follow-up is recommended for a baby whose mother takes anti-HIV drugs during pregnancy. The study staff will talk to you about your choices for long-term follow up. The pregnancy will be reported to federal monitoring agencies.

Are There Benefits to Taking Part in This Study?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. 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.

What Other Choices Do I Have Besides This Study?

Instead of being in this study you have the choice of:

- treatment with prescription drugs available to you
- treatment with experimental drugs, if there is another study available to you and you qualify for that study

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- no treatment

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

What About Confidentiality?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include the FDA, University of Pennsylvania IRB, OHRP, National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

What Are the Costs To Me?

RAL and DRV will be provided by the study. RTV is not provided by the study and will have to be obtained through a non-study prescription. If you do not have insurance, the social worker of the clinic will link you to special funds to provide the medications for people who cannot afford them, if you do not qualify for Ryan White funds, then you may be referred to the City clinic, which provides free care and medications for HIV infected patients.

Taking part in this study may lead to added costs to you and your insurance company. You and/or your health insurance may be billed for the costs of medical care during this study if these expenses would have happened even if you were not in the study, or if your insurance agrees in advance to pay. In some cases it is possible that your insurance company will not pay for these costs because you are taking part in a research study. If the expenses are directly related to research, then the costs associated with these procedures and/or tests will be reimbursed through the Clinical Trials Unit.

Will I Receive Any Payment?

You will be compensated \$5 for the screening and pre-entry visits to cover the cost of transportation to the clinic. At enrollment and for every study visit thereafter, you will be compensated \$25 (cash). Thus, if you attend screening, pre-entry and the 9 scheduled visits, the maximum compensation you will receive from the study is \$235. There is no other form of compensation available such as reimbursements for parking, tokens or child care available.

Additionally, if you do not get your prescriptions through Medicare or Medicaid, you may be eligible to get reimbursed for your co-payments for Ritonavir. To process the request for reimbursement we MUST HAVE YOUR ORIGINAL RECIEPT from the pharmacy that includes information such as your name, the name of the drug and the amount you paid. You will be reimbursed upon presentation of

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a valid receipt in cash for amount UP TO fifty (\$50) dollars. If you have already been randomized to the study and have paid a co-payment for ritonavir and still have your receipt, you will be eligible to receive this reimbursement.

What Happens If I Am Injured?

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. 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. There is no program for compensation either through this institution or the National Institutes of Health. 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.

You do not give up your legal rights by signing this form.

What Are My Rights As a Research Subject?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your healthcare provider will treat you the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

What Do I Do If I Have Questions Or Problems?

For questions about this study or a research-related injury, contact:

- Pablo Tebas, MD (215-349-8092)
- Clinical Trials Unit (215 349-8092)

For questions about your rights as a research subject, contact:

- Director of Regulatory Affairs at the University of Pennsylvania by phoning (215) 898-2614

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CONSENT

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 Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine 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. You will also be given the University of Pennsylvania Health System and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your health information.

Name of Subject (Please Print)	Signature of Subject	Date
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Name of Person Obtaining Consent (Please Print)	Signature	Date
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For subjects unable to give authorization, the authorization is given by the following authorized subject representative:

Authorized subject representative [print]	Authorized subject representative Signature	Date
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Provide a brief description of above person authority to serve as the subject's authorized representative.
