

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

Gilead Sciences, Inc.; GS-US-183-0145; Amendment 3 August 5, 2009

A Multicenter, Randomized, Double-Blind, Double-Dummy, Phase 3 Study of the Safety and Efficacy of Ritonavir-Boosted Elvitegravir (EVG/r) Versus Raltegravir (RAL) Each Administered With a Background Regimen in HIV-1 Infected, Antiretroviral Treatment-Experienced Adults

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Your contacts at the Hospital of the University of Pennsylvania, Philadelphia for this study are:

Principal Investigator:	Pablo Tebas, MD	(215) 349-8092
Coordinator:	Joseph Quinn, RN	(215) 349-8092
Study Nurse:	Wayne Wagner, RN	(215) 349-8092

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

You have been asked to volunteer for a clinical research study involving an experimental drug named elvitegravir for the treatment of HIV-1 infection. An experimental drug means that the United States Food and Drug Administration (FDA) has not approved it for use by the general public.

This consent form may contain words you do not understand. Please ask the study doctor or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this clinical research study.

YOUR RIGHTS

This consent form tells you about the study. Your study doctor or study nurse will go over this with you and answer any questions you may have regarding this research study. If you agree to volunteer, you will be asked to sign and date this consent form. You will be given a copy of the signed and dated consent form to keep.

No one can force you to take part in this study. Even if you agree to participate now, you are free to change your mind and stop at any time without penalty or loss of benefits to which you would otherwise be entitled.

Before you agree to volunteer, you must understand the purpose of the study, how your participation may help you, any potential risks to you, and what is expected of you during the study.

DISCLOSURE OF MONEY RECEIVED OUTSIDE OF THE STUDY:

This research study is supported by money from Gilead Sciences, Inc.. In addition, the person leading this research study receives payment from Gilead Sciences, Inc. for activities that are not a part of this study. These activities may include consulting, advisory board membership, giving speeches or writing reports. If you would like more information, please ask the researchers or the study coordinator.

PURPOSE OF THE STUDY

With an estimated 33 million people in the world infected with the virus, HIV is a major medical problem. The purpose of this study is to determine if elvitegravir (which is one of a new class of anti-HIV medications called integrase inhibitors) is safe and effective when given in combination with a background regimen (or "BR" for short) in subjects who are failing their current regimen of HIV medications. A "regimen" is considered to be all the anti HIV medications that you are taking or you will be taking to fight your HIV infection. The safety and effectiveness of elvitegravir will be compared

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with that of a similar integrase inhibitor called raltegravir that has been approved by the FDA. The dose used in this study for raltegravir is the dose that has been approved. The safety and how well these drug combinations are tolerated will be determined based on vital signs (i.e., heart rate, breathing rate, body temperature, and blood pressure), physical exams, laboratory tests and questions about any problems you might experience during the study. As part of this study, levels of HIV-1 in the blood ("viral load") and drug levels of elvitegravir and raltegravir will be measured at various times during the study.

DESIGN OF THE STUDY

If you agree to participate in this research study, you will be one of 700 subjects recruited from about 230 study sites in the United States, including Puerto Rico, Europe, Australia, Canada and Mexico. It is expected that approximately 5-10 people will participate in this study at the University of Pennsylvania.

This is a double-blind study, which means that neither you nor your study doctor will know which study drug you are receiving. You will be enrolled in the study into one of two treatment arms to receive either elvitegravir 150 mg or raltegravir 400 mg. Elvitegravir must be taken with ritonavir. Because you will be taking a ritonavir-boosted protease inhibitor (PI), a class of HIV drugs, as part of your BR, you will take elvitegravir together with ritonavir and the PI that is prescribed by your study doctor. You will receive three tablets of study drug per day, in addition to your BR medications. Of these three study drug tablets, one of the drugs will be active (elvitegravir or raltegravir). The remaining tablet(s) will be placebo, which means it contains material with no active effect on your HIV but looks like the equivalent active study drug. This is also a randomized (by chance, like a flip of a coin) study, so you will be selected to receive one of the two treatments listed below:

Treatment Arm 1: elvitegravir 150 mg once a day + raltegravir placebo twice a day + BR

Treatment Arm 2: raltegravir 400 mg twice a day + elvitegravir placebo once a day + BR

You will have a 1 out of 2 chance of being assigned to each of the treatment arms. Again, your treatment arm assignment will not be known to you or your doctor.

Your study doctor will choose your BR treatment regimen based on the anti-HIV drugs you have taken in the past and the screening results of viral resistance testing (genotype/phenotype). The BR will be made up of a fully-active ritonavir-boosted PI and a second drug. The following ritonavir-boosted PIs are allowed for use in this study: Aptivus[®] (tipranavir), Kaletra[®] (lopinavir/ritonavir), Lexiva[®] (fosamprenavir), Prezista[™] (darunavir) or Reyataz[®] (atazanavir). For some HIV medicines, taking a low dose of ritonavir increases ("boosts") the effectiveness of the HIV medicine.

The second drug may or may not be fully-active and can be one nucleoside or nucleotide reverse transcriptase inhibitor (NRTI), etravirine, maraviroc, T-20 or one of three fixed-dose combination therapies Combivir[®], Truvada[®], or Kivexa[®]/Epzicom[®]. However, the second drug must not be efavirenz, nevirapine, or delavirdine (due to unknown pharmacokinetic interactions); an integrase inhibitor; or any of the combination drugs Atripla[™] or Trizivir[®].

If you are randomized to receive elvitegravir and you are taking either Kaletra[®] (lopinavir/ritonavir) or Reyataz[®] (atazanavir) as part of your BR, you will receive a lower dose of elvitegravir (85 mg).

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Once you are confirmed to be eligible to participate in the study, and you state that you want to take part in the study, you will be assigned a unique subject number.

Elvitegravir and raltegravir will be supplied by Gilead Sciences, Inc., the Sponsor of this study. If your study doctor decides to use tenofovir disoproxil fumarate (tenofovir DF), also known as VIREAD[®], as part of your BR, this will also be supplied by Gilead Sciences. All other medications chosen as part of your BR, including ritonavir, will be your responsibility, and supplied by your local pharmacy or your study doctor. The study drugs supplied by Gilead Sciences, Inc. must be stored at room temperature. Your study doctor or study nurse will inform you as to the proper storage of all other drugs used in this study.

If you are a subject who has screened or previously enrolled into Study GS-US-183-0144 and are now rolling over into the GS-US-183-0145 study, you will continue to attend your regular scheduled visits as outlined below.

DURATION OF THE STUDY

The screening period (the time between the screening visit and baseline visit) may last up to 56 days. You will be treated with the study drug(s) for a minimum of 48 weeks (11 months). During this time, you will be required to visit the clinic at least 13 times. Following your 48 weeks on-study, you will continue to take your study drug and attend visits every 8 weeks until the study is unblinded. Subjects who complete the required on-study treatment and who qualify will be offered the opportunity to receive open-label elvitegravir as part of a separate roll-over study and may not have to come for the 30-Day Follow-up Visit for this study.

STUDY PROCEDURES

Screening

To help the study doctor determine your eligibility and safety to participate in this study, you need to be seen at the clinic within 56 days before the study starts. After you consent and you receive a copy of the informed consent form, you will have several screening procedures done. These procedures will include:

- a. An interview about your medical history, including any illnesses or health problems, and your history of HIV-1 disease-related events and any current or prior HIV medications
- b. A complete physical examination, including vital signs (blood pressure, temperature, breathing rate, and heart rate), weight and height
- c. A urine sample for standard laboratory tests
- d. If you are a female able to become pregnant, a blood pregnancy test will be required. If the blood test is positive, you will not be eligible to participate in the study.
- e. About 4 teaspoons (20 mL) of blood will be taken for general health screening tests, such as chemistry and blood count, and to determine the amount of HIV-1 in your blood.
- f. About 1 teaspoon (6 mL) of blood will be drawn for an HIV-1 genotype/phenotype test. Genotype testing is a technique that finds changes or "mutations" in certain regions of the HIV-1 gene. Phenotype testing is a technique used to determine whether a mutation in the HIV-1 gene changes how anti-HIV drugs affect the HIV-1 virus. Some mutations can prevent certain anti-HIV drugs or drug regimens from reducing the level of HIV-1 in your blood. When this occurs, the HIV-1 has become "resistant" to that drug and possibly other similar

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drugs. The genotype and phenotype tests will help your doctor decide the best medicines to prescribe for you and to compose your BR while you participate in this study. Your screening time may be extended up to 56 days if your study doctor requires you to repeat the genotype/phenotype test.

- g. A 12-lead ECG (electrocardiogram) to check the functioning of your heart.

The study doctor will review all of your medical information and findings from your screening visit (including medical history, medications, clinical laboratory results, physical exam, etc.) and other entry criteria, as required by the study protocol, to determine if you are eligible to participate in this study.

Pre-Baseline

Once you are found to be eligible, you may come back to the clinic between 1 and 14 days before the Baseline visit for the "Pre-Baseline" visit. It may be possible for you to participate in the Pre-Baseline visit over the telephone. At this visit you will be randomized into the study and you will be prescribed your BR. It is very important that you do not take any of the prescribed medications until after all of the required study procedures at the Baseline visit have been completed.

At the Pre-Baseline visit, you will also be asked whether there has been any change in your health (illness or health problems) since the screening visit and whether you have used any medications since then, other than those you named at the screening visit.

Restrictions during the Study

You will be told not to eat or drink anything (except water) for at least 8 hours before your blood is drawn at the Baseline Visit, Weeks 24, 48, and every 24 weeks (post-week 48 visit).

You cannot take any antacids that contain calcium, magnesium, or aluminum (for example, Tums[®] or Roloids[®]), Carafate[®] (an ulcer medicine), or vitamins/mineral supplements that contain calcium, iron or zinc for a minimum of 2 hours before or 2 hours after any dose of study drug. You must check with the study doctor before taking any medication or health supplements for the length of the study.

Baseline/Day 1

You will be asked to come back to the clinic within 56 days after the Screening visit for the "Baseline" (Day 1) visit. The following procedures will occur during this visit:

- a. You will be asked whether there has been any change in your health (illness or health problems) and whether you have taken any new medications since your last visit.
- b. A complete physical examination, including vital signs and weight
- c. A urine sample for standard laboratory tests
- d. If you are a female able to become pregnant, a urine pregnancy test will be required. If the urine pregnancy test is positive, you will have a blood pregnancy test to confirm the result. If the blood test is positive, you will not be enrolled into the study.
- e. About 3 teaspoons (about 15 mL) of blood will be taken for chemistry, complete blood count, CD4+ cell count (white blood cell that fights infection), tests for hepatitis B virus, hepatitis C virus and to determine HIV-1 levels in your blood.
- f. About 1 teaspoon (about 6 mL) of blood will be collected and stored to allow the possibility of conducting tests at a later date (for example, to check whether the HIV in your blood can develop resistance to this anti-HIV drug).

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- g. Tests on blood being drawn at this visit will be used to measure changes in the amount of sugar and fats in your blood. About 1 teaspoon (about 4 mL) of blood will be taken for this test. **It is important that your blood is drawn for this sample in the morning prior to eating (in a fasting state). If you have not fasted, you will be asked to return to the clinic within 72 hours in a fasted state. "Fasting" means that you will not eat or drink anything, except water, for at least eight hours before your blood is drawn.**
- h. You will be counseled regarding the importance of taking all study medications.
- i. You will receive a 4-week supply of study drug at this visit. The study drugs should be taken at the same time every day with food and with the BR medications and the ritonavir-boosted PI. You will be responsible for picking up the other medicines that make up your BR. You should pick up these medicines before or during this visit.

It is very important that you do not take any of the prescribed medications until after all of the required study procedures at the Baseline visit have been completed.

Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48

The following procedures will occur during these visits:

- a. You will be asked whether there has been any change in your health (illness or health problems) and whether you have taken any new medications since your last visit.
- b. A physical examination, including vital signs and weight (a complete physical examination will be performed at Weeks 24 and 48 and at the Early Study Drugs Discontinuation visit; a symptom directed physical examination will be performed at all other visits as needed).
- c. A urine sample for standard laboratory tests
- d. If you are a female able to become pregnant, a urine pregnancy test will be required. If the urine pregnancy test is positive, you will have a blood pregnancy test to confirm the result. If the blood test is positive, you will be withdrawn from the study and asked to return for a follow-up visit.
- e. About 3 teaspoons (about 15 mL) of blood will be taken for chemistry, complete blood count, CD4+ cell count and to determine HIV-1 levels in your blood.
- f. About 1 teaspoon (about 6 mL) of blood will be collected and stored to allow the possibility of conducting tests at a later date (for example, to check whether the HIV in your blood can develop resistance to this anti-HIV drug and to measure the amount of drug in your blood).
- g. Blood being drawn at the Weeks 24 and 48 visits will be used to measure changes in the amount of sugar and fats in your blood. About 1 teaspoon (about 4 mL) of blood will be taken for this test. **It is important that your blood is drawn for this sample in the morning prior to eating. If you have not fasted, you will be asked to return to the clinic within 72 hours in a fasted state. "Fasting" means that you will not eat or drink anything, except water, for at least eight hours before your blood is drawn.**
- h. At your Week 2, 12, 16, 24, and 48 visits, about 1 teaspoon (about 6 mL) of blood will be taken to measure the amount of elvitegravir or raltegravir in your blood. This type of testing is called pharmacokinetics (PK) and measures the amount of the study drug in your blood. It tells the researchers how much time it takes for the study drug to be absorbed into your body and how long it stays in your body after it has been absorbed. **For this test to be accurate it is important that you take your study drugs AFTER your blood sample has been taken.**
- i. At your Week 8, 20, 32, and 40 visits about 1 teaspoon (about 6 mL) of blood will be taken to measure the amount of elvitegravir or raltegravir in your blood for PK. **You do not need to wait to take your study drug prior to these visits.**

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- j. For the Week 4 visit only, an intensive PK blood sample will be collected at the following timepoints: pre-dose, 1 hour post-dosing, and 24 hours post-dosing. There will be an option for you to choose to complete blood sampling at 2, 3, and 4 hours post-dosing as well. About 1 teaspoon (about 6 mL) of blood will be drawn for each time point. **For this test to be accurate it is important that you take your study drugs AFTER your pre-dose blood sample has been taken.**
- k. Subjects meeting the definition of suboptimal virologic response (your viral load does not drop sufficiently enough) will have samples sent for HIV-1 RNA testing and blood drawn for HIV-1 genotype/phenotype testing (a test which determines if the HIV treatment you are currently taking is still working against the HIV virus) at the Week 12 visit. Suboptimal virologic response means you have HIV-1 RNA higher than 50 copies/mL and have had less than a 1 log₁₀ reduction in HIV-1 RNA from baseline at the Week 8 visit. The study doctor will then decide to either switch your BR with or without study drug. You will remain on study until the end of the study even if this happens.
- l. Subjects meeting the definition of virologic rebound (your viral load returns to the level it was at when you started the study) will be required to return to the clinic for a scheduled or unscheduled visit to confirm whether or not you are truly failing your treatment. Virologic rebound means that the HIV-1 levels in your blood have been detected again after having been undetectable at earlier visits. About 2 teaspoons (about 12 mL) of blood will be drawn during this visit. The study doctor will then decide to either switch your BR with or without study drug. You will remain on study until the end of the study even if this happens.
- m. You will be counseled regarding the importance of taking all study medications.
- n. You will receive a 4-week supply of study drug at the Weeks 4, 8, 12, 16 and 20 visits. You will receive an 8-week supply of study drug beginning at the Week 24 visit and continuing every 8 weeks until the end of the study. The study drugs should be taken at the same time every day **with food** and **with the BR medications and the ritonavir-boosted PI**. You will be responsible for picking up the other medicines that make up your BR. You should pick up these medicines before or during each study visit.
- o. You will be required to bring your study drug bottles back to the clinic at each visit (with the exception of your Week 2 visit).

Every 8 weeks Following Week 48

The following procedures will occur during these visits:

- a. You will be asked whether there has been any change in your health (illness or health problems) and whether you have taken any new medications since your last visit.
- b. A physical examination (complete physical examination will be performed every 24 weeks and at the Early Study Drugs Discontinuation visit), including vital signs and weight; a symptom directed physical examination will be performed at all other visits as needed.
- c. A urine sample for standard laboratory tests
- d. If you are a female able to become pregnant, a urine pregnancy test will be required. If the urine pregnancy test is positive, you will have a blood pregnancy test to confirm the result. If the blood test is positive, you will be withdrawn from the study and asked to return for a follow-up visit.
- e. About 3 teaspoons (about 15 mL) of blood will be taken for chemistry, complete blood count, CD4+ cell count and to determine HIV-1 levels in your blood.

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- f. About 1 teaspoon (about 6 mL) of blood will be collected and stored to allow the possibility of conducting tests at a later date (for example, to check whether the HIV in your blood can develop resistance to this anti-HIV drug and to measure the amount of drug in your blood).
- g. Tests on blood drawn every 24 weeks will be used to measure changes in the amount of sugar and fats in your blood. About 1 teaspoon (about 4 mL) of blood will be taken for this test. It is important that your blood is drawn for this sample in the morning prior to eating. If you have not fasted, you will be asked to return to the clinic within 72 hours in a fasted state. "Fasting" means that you will not eat or drink anything, except water, for at least eight hours before your blood is drawn.
- h. Subjects meeting the definition of virologic rebound will be required to return to the clinic for a scheduled or unscheduled visit to confirm whether or not you are truly failing your treatment. Virologic rebound means that the HIV-1 levels in your blood have been detected again after having been undetectable at earlier visits. About 2 teaspoons (about 12 mL) of blood will be drawn during the unscheduled visit. The study doctor will then decide to either switch your BR with or without study drug. You will remain on study until the end of the study.
- i. You will be counseled regarding the importance of taking all study medications.
- j. You will receive an 8-week supply of study drug beginning at the Week 48 visit and continuing every 8 weeks until the end of the study. The study drugs should be taken at the same time every day with food and with the BR medications and the ritonavir-boosted PI. You will be responsible for picking up the other medicines that make up your BR. You should pick up these medicines before or during each study visit.
- k. You will be required to bring your study drug bottles back to the clinic at each visit.

Early Study Drugs Discontinuation Visit

If you discontinue from the study at any time before the study is complete, you will be asked to return to the study center within 72 hours of stopping study drugs. For safety purposes, you will be asked to continue to come to the scheduled study visits through the end of the study. Procedures at this visit will include:

- a. You will be asked whether there has been any change in your health (illness or health problems) and whether you have taken any new medications since your last visit.
- b. A complete physical examination, including vital signs and weight
- c. A urine sample for standard laboratory tests.
- d. If you are a female able to become pregnant, a urine pregnancy test will be required. If the urine pregnancy test is positive, you will have a blood pregnancy test to confirm the result.
- e. About 3 teaspoons (about 15 mL) of blood will be taken for complete blood count, chemistry, CD4+ cell count and to determine HIV-1 levels in your blood.
- f. About 1 teaspoon (about 6 mL) of blood will be collected and stored to allow the possibility of conducting tests at a later date (for example, to check whether the HIV in your blood can develop resistance to this anti-HIV drug and to measure the amount of drug in your blood).
- g. About 2 teaspoons (about 12 mL) of blood may be drawn for an HIV-1 genotype/phenotype test.
- h. You will be required to bring your study drug bottles back to the clinic.

30-Day Follow-Up

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If you discontinue your study medication, you will be asked to return to the study center 30 days after the completion of the Early Study Drugs Discontinuation visit. Procedures at this visit will include:

- a. You will be asked whether there has been any change in your health (illness or health problems) and whether you have taken any new medications since your last visit.
- b. A symptom-driven physical examination, including vital signs and weight
- c. A urine sample for standard laboratory tests.
- d. If you are a female able to become pregnant, a urine pregnancy test will be required. If the urine pregnancy test is positive, you will have a blood pregnancy test to confirm the result.
- e. About 3 teaspoons (about 15 mL) of blood will be taken for complete blood count, chemistry, CD4+ cell count and to determine HIV-1 levels in your blood.
- f. Should any of your evaluations show abnormal results, you may be asked to return to the study center to repeat the test until it returns to normal or baseline.

STORAGE OF BLOOD SAMPLES

A portion of your blood sample drawn at visits Baseline (Day 1), Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, every 8 weeks post-Week 48, and Early Study Drugs Discontinuation will be frozen and stored. Your stored blood samples and the information collected about you during the study may be used by the Sponsor or its research partners for HIV-1 genotyping/phenotyping assays or their development, for retesting the amount of HIV-1 in your blood, for measurement of antiviral drug levels in your blood, or for future testing to learn more about how the study drug has worked against HIV-1 in your blood.

The way the HIV virus becomes resistant to the medicines we use to treat it is by changing its genetic information, so the drugs may no longer work. The way to detect if this has happened is to do a genotype or a phenotype of your HIV virus. Genotype testing detects changes or "mutations" in certain regions of the HIV-1 genome. Phenotype testing is used to determine whether a mutation in an HIV-1 gene changes how anti-HIV drugs affect the HIV-1 virus. Some mutations can prevent certain anti-HIV drugs or drug regimens from reducing the level of HIV-1 in your blood. When this occurs, the HIV-1 has become "resistant" to that drug and possibly other similar drugs. Genotype and phenotype tests may be experimental; that is, these tests may not have been approved by the FDA. The test results may not have direct benefit to you. At the conclusion of this study, these samples may be retained in storage by Gilead Sciences, Inc. for a period up to 10 years.

No human genetic testing will be performed without your expressed consent.

RISKS and BENEFITS

ELVITEGRAVIR COMMON SIDE EFFECTS

Elvitegravir has only been given to a small number of human subjects, and therefore information on the side effects in humans is limited at this time. As of February 18, 2009, 307 HIV-infected subjects and 788 non HIV-infected subjects have been given elvitegravir. In these studies, mild headache was the most common side effect. Subjects also had mild diarrhea, mild vomiting, mild fatigue, mild nausea, mild loss of appetite, and dizziness.

The reported side effects of elvitegravir in HIV patients also include diarrhea, nausea, constipation, fatigue, hypersensitivity (allergic reaction), upper respiratory tract infection, hypertension, headache, and difficulty sleeping.

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ELVITEGRAVIR IN COMBINATION WITH RITONAVIR SIDE EFFECTS

Elvitegravir was given in combination with ritonavir in a study with 12 non HIV-infected subjects over 10 days at a total daily dose of 200 mg. Review of safety data from the study with elvitegravir and ritonavir has identified no significant adverse events or laboratory abnormalities. The most common side effects of elvitegravir given in combination with ritonavir are mild nausea, dizziness, headache, pruritus (itching) and vomiting.

PROTEASE INHIBITORS AND NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS SIDE EFFECTS

Some major concerns linked with PIs include abnormal increases in blood cholesterol and triglyceride levels, abnormal body fat redistribution, and an increase in blood sugar. The most common side effects of PIs include nausea, diarrhea and abdominal discomfort. Other less common side effects include increases in liver function tests, rash, muscle pain or headaches. In addition, each PI may be linked with its own unique side effects. Please ask your study doctor for more specific information.

Lactic acidosis (increase in lactate levels, the symptoms of which include of nausea, vomiting, abdominal pain, general discomfort and tiredness that doesn't get better) and severe hepatomegaly (enlargement of the liver) with steatosis (fatty deposits) have been reported. There have also been reports of fatal cases with the use of NRTI, another class of anti-HIV drugs taken alone or in combination with other anti-HIV drugs. A majority of these cases have been in women. Obesity and taking nucleoside drugs for a long time may be risk factors. Patients with known risk factors for liver disease may be at greater risk; however, cases have also been reported in patients with no known risk factors. If you experience any of these symptoms, you should contact your study doctor.

RALTEGRAVIR COMMON SIDE EFFECTS

The dose of raltegravir being used in this study has been approved by the FDA. Adverse events most commonly linked with raltegravir are nausea, headache, tiredness, and weakness. Other side effects include rash, severe skin reactions, depression, and suicidal thoughts and actions. In addition, subjects who have taken raltegravir have experienced a condition known as lipodystrophy, a disorder of the metabolism of fat in your body which may cause a loss of fat in some of your body tissue.

Call your study doctor right away if you experience unexplained muscle pain, tenderness, or weakness.

These are not all the side effects of raltegravir. Please talk to your study doctor for more details on side effects or refer to the raltegravir package insert for additional information.

TENOFOVIR DF COMMON SIDE EFFECTS

Tenofovir DF has been studied in approximately 12,000 HIV-infected adults for as long as 204 weeks in some patients. Common potential side effects identified in patients who received at least one dose of tenofovir DF 300 mg include diarrhea, nausea, vomiting, flatulence (intestinal gas), and dizziness. Those side effects were often mild or moderate in severity, and did not lead to discontinuation of tenofovir DF. Of these events, only vomiting and flatulence (intestinal gas) were more common for patients taking tenofovir DF than those taking placebo (sugar pill). Additionally, the following side effects have been reported in HIV-infected patients treated with combination therapy that has included tenofovir DF and other anti-HIV drugs: weakness, abdominal pain, allergic reaction including potentially serious, swelling of the face, lips, and/or tongue, with or without rash, pancreatitis

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(inflammation of the pancreas), high levels of amylase in the blood, shortness of breath, rash, abnormalities of tests that measure hepatic (liver) function and hepatitis (inflammation of liver).

Additionally, cases of lactic acidosis (high levels of lactic acid in the blood), liver problems with enlargement of the liver and fat in the liver, including fatal cases, were reported in HIV-infected patients treated with anti-retroviral agents similar to tenofovir DF. The symptoms of lactic acidosis include: weakness, unexpected and uncommon abdominal pain, nausea and vomiting. Symptoms of liver problems include; yellowing of the skin or whites of the eyes, dark urine, light colored bowel movements, loss of appetite, nausea and lower abdominal pain. If you notice any of these symptoms, please request medical assistance immediately.

Cases of kidney damage have been reported in patients taking tenofovir DF who already have circulatory disease or specific kidney disease, and patients who, while receiving tenofovir DF, were also taking medications that may cause damage to the kidneys. Kidney damage has also been reported in patients without any of these factors. For example, some patients have had damage to the structure and function of the kidneys, which may lead to muscle abnormalities, muscular weakness, destruction of muscle tissue, bone pain and fractures due to softening of bones, and low potassium and phosphate in the blood. In addition, death of kidney tissue, continuous or sudden kidney failure, abnormal kidney function, inflammation of the kidneys, protein in the urine, excessive urination, nephrogenic diabetes insipidus (excretion of urine resulting in dehydration and thirst), and increased creatinine in the blood have also been reported in patients taking tenofovir DF.

Bone toxicity, including a decrease in bone mineral density, was seen in animals following treatment with tenofovir DF. Decreases in bone mineral density have been seen in humans. These types of changes may increase the risk of bone fractures, although this has not been seen in human studies.

If you are infected with hepatitis B virus (HBV), there is a possibility of an unexpected worsening of hepatitis B if you stop taking tenofovir DF.

Please talk to your study doctor for more details on side effects or refer to the tenofovir DF package insert for additional information.

IMMUNE RECONSTITUTION SYNDROME

A condition called immune reconstitution syndrome can happen in some patients with advanced HIV infection (AIDS) when combination anti-HIV treatment is started. Signs and symptoms of inflammation from opportunistic infection that a person has or had may occur as the medicines work to control the HIV infection and strengthen immune system. Call your study doctor right away if you notice any signs or symptoms of an infection after starting study medication.

ALLERGIC REACTION RISKS

As with taking any drug, there is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are: rash, difficulty breathing, wheezing, sudden drop in blood pressure, swelling around the mouth, throat or eyes, a fast pulse, and sweating. Please seek treatment and alert the study doctor and study staff immediately if you have any of these symptoms, or any other side effects, during the study.

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If risks are identified while this study is ongoing, you will be told about them in a timely manner. Medical staff are in the clinic to provide medical attention if needed.

BLOOD DRAWS

In addition to risks linked with the study drug(s), drawing blood from a vein may cause local pain, bruising, occasional lightheadedness, fainting, and very rarely, infection at the site of the blood draw.

OTHER

As with all drugs, allergy as well as unexpected or yet unknown side effects may occur. Any new information that becomes known during the study and that may affect your participation will be shared with you by your study doctor.

Viruses that are resistant to elvitegravir and raltegravir may develop during the course of treatment. This may reduce your treatment options in the future. Throughout the study, your study doctor will monitor your HIV-1 levels for viral rebound (increases in HIV-1 levels after having previous results of lowered HIV-1 levels). Resistant mutations develop most rapidly in people who do not adhere to all of the drugs in their anti-HIV drug regimen. 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 end your participation in the study. You should contact your study doctor immediately if you feel that you cannot tolerate your drug regimen.

POSSIBLE BENEFITS OF THE STUDY

There is no guarantee that you will receive personal benefit from participating in this study. The study drugs are not expected to cure you of HIV-1 infection. However, information gained from your participation in this study may help to determine if elvitegravir is effective against HIV-1 and is safe and easy to tolerate. Your participation in this study may benefit the community and scientists and doctors who work with HIV-1 by providing increased knowledge and information about the treatment of your disease.

PREGNANCY AND BREAST FEEDING

The effects of elvitegravir alone or in combination with ritonavir and other HIV medications have not been fully evaluated on the developing fetus in humans. Animal studies do not indicate direct or indirect harmful effects of elvitegravir with respect to pregnancy. Because the effects of elvitegravir on a developing fetus as well as on exposed infants are unknown, any female able to become pregnant (i.e., not surgically sterile or at least two years post-menopausal) must have a negative blood pregnancy test to enroll; females who are breastfeeding will not be enrolled in this study.

It is very important while you are in this study that you do not become pregnant if you are a female, or do not cause others to become pregnant if you are a male. You are aware that not having sex is the only certain way to prevent pregnancy. If you are a sexually active male or female, it is required that you use an effective method of birth control from the screening visit throughout the study and for 30 days following the last dose of study drug. Effective methods of contraception in this study are: two separate forms of contraception, one of which must be an effective barrier method, or be non-heterosexually active, practice sexual abstinence, or have a vasectomized partner (confirmed sterile). If you are a female who is sexually active and able to become pregnant, please speak with your study

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doctor to determine the best method of birth control for you to use during this study. Hormone-based contraceptives may not be effective at preventing pregnancy when they are used with elvitegravir. 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 become pregnant or suspect that you have become pregnant while in the study, you will be required to stop taking all the study drugs and to notify your study doctor immediately. You will be discontinued from the study.

Other not yet identified side effects could occur to you, your embryo or fetus should you become pregnant during the time you participate in the study or after you have completed the study.

CONDOM USE

It has been proven that condom use decreases the risk of spreading HIV and Hepatitis B 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 for all sexual activity to include oral, vaginal, and anal sexual contact. Condom use is recommended in addition to your current form of birth control.

TREATMENT OPTIONS

You have the option to discuss with your study doctor not to participate or to choose other anti-HIV drugs to treat your disease. These medicines include commercially available medicines. Your study doctor will discuss appropriate alternative treatment options with you. You will be made aware of any new findings that become available during the course of the study and that may affect your willingness to participate in this study.

WITHDRAWAL FROM STUDY AND REFUSAL TO PARTICIPATE

Special care will need to be taken when determining if you need to stop the study drug. Your study doctor will supervise any discontinuation of the study drug with your health as the first priority. Your participation in this study may be stopped at any time by a) your study doctor, b) Gilead Sciences, Inc., c) the FDA, d) the Institutional Review Board (a review group that gives approval to your study doctor to conduct this study), and e) other appropriate regulatory agencies.

Your participation in this clinical research study is voluntary, and you can refuse to participate or stop at any time without stating a reason. Your withdrawal will not affect your access to other medical care.

Your study doctor may withdraw you from the study if it is considered important for your medical safety. If it is discovered that you did not give an accurate medical history or did not follow the instructions for the study given by your study doctor and/or study nurse, you may be taken off the study at any time. If you are taken off the study, you will no longer receive the study drugs.

COST OF TREATMENT

The elvitegravir, raltegravir, and tenofovir DF used in this study will be given to you at no cost. All clinic, professional, diagnostic and laboratory fees that are part of this study will also be provided at no cost to you. You or your usual health care payer will be responsible for the BR medications and any other health care costs.

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PAYMENT FOR PARTICIPATION

You will be compensated \$50 (CASH) for each clinic visit you attend to cover transportation costs, parking, child care, etc., and for your time and inconvenience. Thus, if you attend all study visits (14), the maximum compensation you will receive from the study is \$700. If you are requested to come into the clinic for additional visits or to have your blood re-checked, you will also be compensated (\$25) for that visit.

COMPENSATION FOR INJURY

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 direct result of taking the study drug or the study procedures in this research study, please contact the investigator listed on page one of this form.

In the event of any such 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 or the Sponsor. The Sponsor, Gilead Sciences, Inc. will reimburse you or the University of Pennsylvania for the reasonable costs of any medical treatment of a study-related injury or illness *provided* that you have followed the instructions of the study doctors. Other than reimbursement of medical treatment expenses, the Sponsor has no plans to provide any other form of compensation for study-related injury or illness. 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.

STATEMENT OF PRIVACY

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records. Please refer to the separate "HIPAA Privacy Authorization" document that explains more specifically how your personal information will be protected.

If you take part in this study, your personal information, including information about your health, will be collected by the study doctors and recorded on study record forms. The study record forms will not contain your name or address but will contain initials, date of birth and a code number. The code number list will be held by the study doctor. Biological samples, including blood samples, that are collected during the study will be analyzed and stored for possible future testing. All information collected or learned about you during the course of this study will be treated as strictly confidential. The study records and biological samples will be analyzed by the Sponsor and may be shared with its research partners; however, any data or information learned from the study that is to be reported in scientific reports, journals, or published materials by the Sponsor or its research partners, will not include any personal information identifying you as a subject in a study. The Sponsor may also wish to use your personal information and any biological samples taken during this study for future research on

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the prevention, treatment or diagnosis of HIV-1. Gilead Sciences, Inc. will take all reasonable steps to ensure that in any future research on HIV-1 your privacy will be protected.

Representatives from government agencies, institutional review boards, and the Sponsor or its authorized representatives, may also need access to your medical records and study records for the purpose of checking data collected for the study. By signing the separate HIPAA Privacy Authorization, you authorize this access.

The Sponsor may wish to send information or biological samples collected or data learned during this study to its researchers, its research partners or regulatory authorities located in other countries to be analyzed for purposes of this study or for future research into HIV-1. Some countries outside the U.S. may not have laws that provide the same level of protection as laws in the U.S., but Gilead Sciences, Inc. will take all reasonable steps to ensure that your privacy is protected.

CONTACT INFORMATION

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

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.

This Consent Form contains important information to help you decide if you want to be in this study. If you have questions that are not answered in this form, please ask one of the study staff. Please answer the following questions by placing your initials in the line for "Yes" or "No".

1. Have you understood this form? ___ Yes ___ No
2. Have you had the opportunity to ask questions and discuss the study? ___ Yes ___ No
3. Have you received answers you find acceptable to all of your questions? ___ Yes ___ No

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- 4. Have you received enough information about the study to make an informed decision? ___ Yes ___ No
- 5. Do you understand you are free to stop the study at any time without having to give a reason and without affecting your medical care? ___ Yes ___ No
- 6. Do you understand your medical records may be reviewed and how the information will be used? ___ Yes ___ No

If you answered NO to any of the six questions listed above, you should not sign this form. Once you have had all your questions answered and you are comfortable participating in this study, please sign below.

By signing and dating this form you agree that you are volunteering to be in this study.

Name of Subject (Please Print in BLOCK LETTERS)	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's authority to serve as the subject's authorized representative.

- I agree to have my stored blood samples tested by the sponsor as described on page 8 of this consent form.

Name of Subject (Please Print in BLOCK LETTERS)	Signature of Subject	Date
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- I agree to have my blood samples tested by the sponsor for HIV resistance patterns using genotype and phenotype tests as described on page 8 of this consent form.

Name of Subject (Please Print in BLOCK LETTERS)	Signature of Subject	Date
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