UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

Gilead Sciences, Inc. GS-US-216-0130, Amendment 1, 5-OCT-2011

A Phase 3b, Open-label, Single Arm Study to Evaluate the Safety and Efficacy of Cobicistat-boosted Darunavir Plus Two Fully Active Nucleoside Reverse Transcriptase Inhibitors in HIV-1 Infected, Antiretroviral Treatment-Naïve and -Experienced Adults with No Darunavir Resistance-associated Mutations

CONSENT TO PARTICIPATE IN A RESEARCH STUDY AND RESEARCH SUBJECT HIPAA AUTHORIZATION

Your contacts for this study at the Hospital of the University of Pennsylvania [HUP] are:

Site address: 502 Johnson Pavilion, Philadelphia, PA 19104

Principal Investigator:	Pablo Tebas, MD	(215) 349-8092
Manager:	Joseph Quinn, RN	(215) 349-8092
Study Nurses:	Wayne Wagner, RN	(215) 349-8092
	Aleshia Thomas, RN	(215) 349-8092

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

INTRODUCTION

You have been asked to volunteer for a clinical research study involving experimental medications for the treatment of HIV-1 infection. This study is sponsored by Gilead Sciences, Inc. An experimental drug means that the United States Food and Drug Administration (FDA) has not approved it for use by the general public. As part of this study, you will be required to take an experimental combination of medications along with a combination of at least two other medications classified as nucleoside reverse transcriptase inhibitors (NRTIs) which are already approved by the FDA for the treatment of HIV-1 infection.

The experimental combination of medications being evaluated in this study is darunavir and cobicistat and these will be provided by the study. The NRTIs will be decided by the study doctor; if the NRTIs are tenofovir and/or emtricitabine, they will be provided by the study. Other NRTI choices will need to be obtained by prescription and the study will reimburse you.

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 staff will go over this with you and answer any questions you may have regarding this 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. You may stop at any time without penalty or loss of benefits which you would otherwise have.

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.

PURPOSE OF THE STUDY

With an estimated 33.2 million people in the world infected with the virus, HIV is a major medical problem. People who take antiviral medications regularly that stop HIV from replicating can live for

IRB Approved:
From: 03-05-2013 To: 11-04-2013
IC V6 18 FEB 2013
Injury language

many years with HIV infection. People with HIV infection are usually treated with three or four different HIV medications in combination, generally two drugs from the nucleoside reverse transcriptase (NRTI) category plus another active drug in a different category.

The purpose of this study is to see if the combination of Cobicistat (COBI) with darunavir and at least 2 NRTIs is safe, tolerable, and effective in reducing levels of HIV-1 in the blood of subjects who are HIV-1 infected. Darunavir is a protease inhibitor HIV medication approved to treat HIV infection and is always taken with ritonavir. Ritonavir is a drug that acts as a "booster" for darunavir so that smaller doses of darunvavir are needed to be effective against HIV. Cobicistat (COBI) does not have anti-HIV activity when taken alone but acts like ritonavir as a "booster" drug .Thus, this study will determine if COBI is a safe and effective replacement for ritonavir.

The safety and how well this drug combination is tolerated will be determined based on 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 and drug levels of COBI and darunavir will be measured at various times during the study.

DESIGN OF THE STUDY

If you agree to participate, you will be one of 300 subjects recruited from about 60 study sites in United States, Puerto Rico, and, Europe. At Penn, about 5-7 people are expected to participate.

This is an open-label study, which means that you and your study doctor will know exactly what medications you are taking.

All patients on study will receive Cobicistat (COBI) 150 mg + darunavir (DRV) 800 mg + 2 NRTIs. Your study doctor will decide which medication combination is best for your treatment.

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 subject number.

COBI, darunavir, and Truvada (the NRTI combination of emtricitabine and tenofovir), if prescribed, will be supplied by Gilead Sciences, Inc., the Sponsor of this study and must be stored at room temperature. If your doctor or the study doctor recommend NRTIs other than Truvada,these will be reimbursed by the Sponsor. Your study doctor or study nurse will review the proper storage of all study drugs used in this study with you. **The study drugs COBI and darunavir must be taken once a day at the same time every day with food.** It is very important that you take your study drugs every day as instructed by the study doctor.

DURATION OF THE STUDY

The screening period (the time between the Screening Visit and Baseline Visit) may last up to 35 days. The screening period may be extended to up to 42 days after the Screening Visit if a certain screening test called a genotype HIV resistance test needs to be repeated. Genotype testing detects changes or "mutations" in certain regions of the HIV-1 virus. If mutations are present the virus may be resistant to one or more HIV medications, which means the medications will not work to control the virus. You will be treated with the study drug(s) for a minimum of 48 weeks (12 months). During this time, you will be required to visit the clinic at least 11 times. Following your 48 weeks of treatment, you will be given the option to participate in an open-label extension study to receive darunavir, cobicistat and investigator selected NRTIs and attend visits every 12 weeks until cobicistat becomes available for sale in the United

States or until Gilead Sciences elects to terminate the development of cobicistat (whichever comes first).

If you have discontinued study drugs,darunavir and cobicistat prior to Week 48 and are continuing to receive investigator selected NRTIs during the treatment period of the study, at week 48 you will not have the option to participate in the open-label rollover and your participation in the study will end.

STUDY PROCEDURES

Described below are the evaluations and tests that are required at each study visit. Your results will be provided to your care provider at the completion of each visit and your care provider may choose to use them for regular care. Tests performed outside the study will not be able to be used for the study.

Screening

To help the study doctor determine your eligibility and safety to participate in this study, you need to be seen at the study center. After you sign the informed consent form and receive a copy of the informed consent form, you will have several screening procedures done. Note that all of the procedures listed below may not be performed if at any point during the evaluation you no longer meet study entry requirements. These procedures will include:

- An interview about your medical history, including any illnesses or health problems, your history of HIV-1 disease-related events, any treatment for HIV-1 disease, and prior medications within 30 days.
- A complete physical examination, weight, and height.
- A urine sample for laboratory tests.
- 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.
- If you are a female and are post-menopausal, a blood test will be required to confirm your post-menopausal status.
- About 21 mL (about 4 teaspoons) (5 mL = 1 teaspoon) of blood will be taken for general health screening tests and tests related to your HIV, such as chemistry, complete blood count, CD4+ (white blood cell that fights infection) cell count, glomerular filtration rate [(GFR) measures your level of kidney function], tests for hepatitis B virus, hepatitis C virus, and to measure the amount of HIV-1 in your blood.
- About 12 mL (about 2 teaspoons) of blood will be drawn for an HIV-1 genotype test.
- 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.

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, at the Weeks 12, 24, and 48 visits and every 12 weeks after Week 48. (This is referred to as "fasting").

Baseline/Day 1

You will be asked to come back to the study center within 35 days after the Screening visit for the "Baseline" (Day 1) visit. The following procedures will occur during this visit:

- 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.
- A complete physical examination and weight.
- A urine sample for laboratory tests. Some of this urine will be stored to conduct possible clinical testing in the future.
- 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 not be dispensed drug at this visit. You will have a blood pregnancy test to confirm the result of the urine pregnancy test. If the blood test is positive, you will not be allowed to participate in this study.
- About 21 mL (about 4 teaspoons) of blood will be taken for testing of chemistry, complete blood count, eGFR, CD4+ cell count and to determine HIV-1 levels in your blood.
- 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 4 mL (about 1 teaspoon) of blood will be taken for this test. If you have not fasted, you will be asked to return to the study center within 72 hours in a fasted state.
- About 14 mL (about 3 teaspoons) of blood will be collected and stored to allow the possibility of conducting clinical tests at a later date (for example, to check whether the HIV in your blood can develop resistance to your study drug).
- You will be counseled regarding the importance of taking all study medications.
- You will receive a 4-week supply of study drugs. You will begin to take your study drug within 24 hours of the Baseline Visit.

Weeks 2, 4, 8, 12, 16, 24, 36, 48 and every 12 weeks following through the end of the study

You will be asked to return to the clinic for study visits at Weeks 2, 4, 8, 12, 16, 24, 36, and 48. After the Week 48 visit, you will be asked to continue coming in for study visits every 12 weeks. After the last study treatment visit, you will complete a 30 day follow-up visit.

The following procedures will occur during these visits:

- 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.
- A physical examination that will depend on your symptoms and weight (Complete physical exam for Weeks 24 and 48).
- A urine sample for laboratory tests. Some of this urine will be stored at all visits to conduct possible clinical testing in the future.
- 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, your study drug treatment will be discontinued.
- About 18 mL (about 4 teaspoons) of blood will be taken for testing of chemistry, complete blood count, eGFR, CD4+ cell count, and to determine HIV-1 levels in your blood.
- Tests on blood being drawn at Weeks 12, 24, and 48 and every 12 weeks after Week 48 will be used to measure changes in the amount of sugar and fats in your blood. About 4 mL (about 1 teaspoon) of blood will be taken for this test. If you have not fasted, you will be asked to return to the study center within 72 hours in a fasted state.
- About 14 mL (about 3 teaspoons) of blood will be collected and stored to allow the possibility of conducting clinical tests at a later date (for example, to check whether the HIV in your blood has developed resistance to one of the anti-HIV drugs).

- For visits from Week 2 through 48, about 6 mL (about 1 teaspoon) of blood will be taken to measure the amount of study drugs 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. On these visit days you will be asked the time and date that you took your last dose of COBI, darunavir, or Truvada (if prescribed).
- If you do not appear to be responding properly to the study drugs, you will be required to return to the clinic to confirm whether or not the medication is working. Approximately 12 mL (about 2 ½ teaspoons) of blood will be drawn during this visit to measure the amount of HIV-1 in your blood and for resistance testing. The study doctor will then decide whether or not a change to your treatment regimen is required.
- You will receive a 4-week supply of study drugs at Weeks 4, 8 and 12 visits. You will receive an 8-week supply of study drugs at the Weeks 16 and will receive 12 week supply of study drugs beginning Week 24 and 36. At the Week 48 visit and every visit until the end of the study, you will receive a 12-week supply of study drugs. **Your study drugs must be taken once a day at the same time every day <u>with food</u>.** You will be counseled regarding the importance of taking all study drugs.
- You will be required to bring your used and unused study drug bottles back to the clinic at each visit (with the exception of your Week 2 visit). The study drug (number of tablets and/or capsules) will be counted. You will be asked about any missed doses since your last visit.

<u>Early Study Drugs Discontinuation Visit</u>

If you discontinue study drugs 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. Procedures at this visit will include:

- 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.
- A complete physical examination and weight.
- A urine sample for laboratory tests. Some of this urine will be stored to conduct possible clinical testing in the future.
- 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.
- About 18 mL (about 4 teaspoons) of blood will be taken for testing of chemistry, complete blood count, eGFR, CD4+ cell count, and to determine HIV-1 levels in your blood.
- About 14 mL (about 3 teaspoons) of blood will be collected and stored to allow the possibility of conducting clinical tests at a later date (for example, to check whether the HIV in your blood can develop resistance to this anti-HIV drug).
- About 12 mL (about 2 ½ teaspoons) of blood may be drawn for genotype/phenotype testing.
- You will be required to bring your used and unused study drug bottles back to the clinic.

<u>30-Day Follow-Up</u>

You will be asked to attend a 30-Day Follow-Up visit in the following cases:

- If you discontinue your study drugs, you will be asked to return to the study center 30 days after the completion of the Early Study Drugs Discontinuation visit . (After discontinuing study drugs if you have continued to attend regularly scheduled visits, you will not be required to come in for a 30 day follow up visit).

- If you complete the study treatment period, you will be asked to return to the study center 30 days after completion of study drugs.

Procedures at this visit will include:

- 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.
- A symptom-directed physical examination and weight.
- A urine sample for laboratory tests. Some of this urine will be stored to conduct possible clinical testing in the future
- 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.
- About 18 mL (about 4 teaspoons) of blood will be taken for chemistry, complete blood count, eGFR, CD4+ cell count, and to determine HIV-1 levels in your blood.
- About 8 mL (about 1 ½ teaspoons) of blood will be collected and stored to allow the possibility of conducting other clinical tests at a later date.

STORAGE OF BLOOD SAMPLES

A portion of your blood sample drawn at each visit will be frozen and stored. These stored blood samples may be used by the Sponsor or its research partners for HIV-1 resistance tests or their development, for retesting the amount of HIV-1 in your blood, for measurement of antiviral drug levels in the blood, for future testing to learn more about how the study drug has worked against HIV-1 or clinical laboratory testing to provide additional clinical data.

There are two types of HIV resistance tests: genotype and phenotype. Genotype testing detects changes or "mutations" in certain genetic regions of the HIV-1 virus. Phenotype testing is used to determine whether a mutation in an HIV-1 gene changes how anti-HIV drugs affect the HIV-1 virus. Genotype and phenotype tests may be experimental; that is, these tests may not have been approved by the FDA. The results of such tests are for research use only, and the interpretation of 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.

STORAGE OF URINE SAMPLES

A portion of the urine samples taken at each visit, except screening, will be frozen and stored. The stored urine samples may be used by the Sponsor or its research partners for possible additional clinical analyses.

RISKS AND BENEFITS

The medication 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 medication side effects, then please ask the study staff.

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 before you start the study and also before starting any new medications while on the study.

RISKS FOR STUDY DRUGS

COBI; Cobicistat Side Effects

As of June 2011, 561 healthy and 400 HIV-1 infected subjects have been dosed with COBI, as an individual agent, in 19 clinical studies conducted to date, including 17 studies in healthy subjects, and 2 studies in HIV-1 infected subjects who took COBI as part of their first HIV treatment. 163 healthy and approximately 750 HIV-1 infected subject have taken COBI as part of a single tablet regimen (STR) containing the four drug combination of elvitegravir, COBI, emtricitabine and tenofovir in 9 clinical studies conducted to date. COBI has only been given to a relatively small number of human subjects, and therefore information on the side effects in humans is limited and there may be unforeseen risks.

In one clinical study, COBI150 mg with darunavir exposure resulted in darunavir levels in the blood that were similar to the FDA-approved combination of darunavir plus ritonavir 100 mg. In two ongoing studies in which approximately 100 HIV-positive subjects are receiving COBI, mild decreases in estimated kidney function were observed. A follow-up study in healthy subjects showed that actual kidney function does not change. This phenomenon is seen with two other commonly used FDA-approved drugs, trimethoprim (an antibiotic) and cimetidine (an antacid). Your kidney function will be closely monitored throughout your participation in this study with blood and urine tests. COBI 150 mg tablets, dosed daily for up to 60 weeks, were generally well tolerated, and did not cause clinically significant toxicities in humans that were identified in animal studies (heart, liver, thyroid abnormalities, and decreased IgG levels).

COBI is similar in chemical composition to an FDA-approved drug called Norvir® (ritonavir), a drug that belongs to a class of anti-HIV agents called protease inhibitors. Because of this, when taking the COBI tablet you may experience some of the same side effects that are observed with ritonavir. Some of the most common side effects of ritonavir are weakness, fatigue, nausea, vomiting, diarrhea, loss of appetite, abdominal pain, changes in taste, headache, dizziness, increase in the fats in the blood, skin rash, and tingling feeling or numbness in hands or feet or around the lips.

Darunavir (Prezista®) with low dose ritonavir (DRV/rtv)Side Effects

DRV was registered in the United States in 2006, and is now registered in more than 100 countries around the world.

The majority of the DRV adverse drug reactions (ADRs) reported during treatment with DRV/rtv in the Phase III trials were mild in severity. In ARV-treatment naïve HIV-1 infected adult subjects, the most frequent (>5%) ADRs of moderate to severe intensity with DRV 800/100 mg q.d. were diarrhea, headache, rash, and abdominal pain.

Skin rash can occur with the use of DRV/rtv , usually develops within the first 4 weeks of treatment with DRV/rtv, is often mild or moderate in severity, often resolves within one week and does not necessarily lead to treatment interruption. However in some cases, the rash has been severe or life-threatening. Cases of severe skin reactions, have been reported in patients taking DRV/rtv in combination with other anti-HIV drugs, as well as other medications, including Stevens-Johnson syndrome (a blistering rash that spreads causing the top layer of your skin to peel and shed), Toxic Epidermal Necrolysis (TEN) (a more

severe and extensive blistering rash that spreads causing the top layer of your skin to peel and shed), and Acute Generalized Exanthematous Pustulosis (skin eruption characterized by the appearance of areas of red skin studded with small blisters). These serious conditions occur very rarely but can cause a severe rash (including the mouth and lips) and fever and could be potentially life threatening. They usually requires immediate admission to the hospital. These conditions usually go away when all medications are stopped. If you develop a rash or any skin abnormality, you should report it to your study doctor immediately.

Different antiretroviral (ARV) drugs, including DRV/rtv, may affect fat and sugar metabolism and may cause diabetes. The most frequently observed laboratory abnormalities with DRV/rtv are increases in blood fats (triglycerides and cholesterol) and sugars (glucose). Rare cases of pancreatitis (swelling of the pancreas that causes abdominal pain and nausea and can be sometimes life threatening) have been reported in patients taking DRV/rtv and other ARV drugs.

Uncommon cases of liver disorders (including inflammation of the liver that can cause fatigue, loss of appetite, nausea, jaundice, dark urine, liver tenderness) have been reported in patients taking DRV/rtv and other ARV drugs. Patients with liver diseases such as hepatitis B and/or hepatitis C may have worsening of their condition. Some of the liver disorders, which occur or worsen when taking DRV/rtv can be severe and might be sometimes life-threatening.

Rare cases of pancreatitis (inflammation of the pancreas which can be sometimes life-threatening) have been reported in patients taking DRV/rtv and other ARV drugs.

Liver and pancreatic function, in addition to other organs' function will be monitored throughout the study.

This list of side effects is not complete. Please ask your study doctor for more information.

NRTI medications

FTC; Emtriva® Side Effects (Emtricitabine)

The most common side-effects seen in patients treated with emtricitabine in combination with other anti-HIV drugs are: headache, diarrhea, nausea, and rash, which were generally mild. Other common side effects with emtricitabine include dizziness, changes in skin color primarily on the palms and/or soles, weakness, difficulty sleeping, abnormal dreams, pain, vomiting, stomach pain, problems with digestion resulting in gastrointestinal discomfort after meals, increased triglycerides (fatty acid), increased bilirubin (a yellowish pigment made when red blood cells are broken down that can make your skin yellow)in the blood, increased glucose(blood sugar) in the blood, allergic reaction, hives, adverse effects on the function of the liver and pancreas, and low white blood cell count. A reduction in your white blood cell count can make you more prone to infection. You may also experience increased creatine kinase (a muscle protein) in the blood. If creatine kinase is increased, you may experience muscle pain and weakness.

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-HIV agents similar to emtricitabine. 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.

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

TDF; Viread® Side Effects
(Tenofovir DF)

Tenofovir DF has been studied in approximately 12,000 HIV-infected adults for as long as 215 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).

In addition to side effects reported from clinical trials the following side effects have also been identified after tenofovir DF was approved 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 (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).

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.

Decreases in bone mineral density have been seen in humans. These types of changes may increase the risk of bone fractures.

Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

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.

FTC/TDF; Truvada® Side Effects (Emtricitabine/Tenofovir DF)

Please refer to the Emtriva® and Viread® side effects described above for side effects associated with Truvada®, a combination medication containing Emtriva® and Viread®.

Other NRTI Side Effects

Please ask your study doctor for information on risks and benefits for the other NRTI medications if your study doctor recommends other NRTI medication other than Emtriva and Viread.

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 infection that a person has or had may occur as the medicines work to control the HIV infection and strengthen immune system.

Autoimmune disorders such as Graves' disease (a disease in which the thyroid produces excessive thyroid hormones), polymyositis (a disease of caused by inflammation leading to weakness of the muscles), and Guillain-Barre syndrome (a disease that occurs when the body's immune system attacks part of the nervous system, leading to nerve inflammation that causes muscle weakness), have also been reported to occur in the setting of immune reconstitution, however, the time to onset is variable and can occur many months after starting treatment. 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.
- 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.

Loss of Benefit of HIV Therapy If You Are Already on Medication

If you are already taking HIV medication, switching therapy could result in the loss of control of virus replication.

RISK FOR STUDY PROCEDURES

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

ECG
After you have an ECG, you may have mild irritation, slight redness, and itching at the places on your skin where the recording patches are placed. You may have to have your chest shaved for this procedure.

Hepatitis B and C Testing Risks
At the Screening visit, you will be tested for hepatitis B and C, and the results of these tests may be reported to your local health authority. You will be told, face-to-face, the results of these tests. Counseling will be available to you if necessary.

Other
As with all drugs, 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 in a timely manner.

Viruses, which are resistant to the study drugs, 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 take all of their HIV-1 drugs. 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. Your participation in this study may benefit the community, scientists and doctors who work with HIV by providing increased knowledge and information about the treatment of your disease. In addition, during your participation you will have close medical monitoring of your health condition by blood tests and other evaluations during clinic visits.

PREGNANCY AND BREAST FEEDING
The effects of COBI and darunavir in combination with 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 COBI or darunavir with respect to pregnancy. Because the effects of COBI and darunavir in combination with other HIV medications on a developing fetus as well as on exposed infants are unknown, any female able to become pregnant must have a negative blood pregnancy test to enroll. A female subject of childbearing potential is a female who has not reached menopause and not had a hysterectomy, ovaries removed or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating. Females who are breast-feeding 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, be vasectomized or have a vasectomized partner.

If you are a female who is sexually active and able to become pregnant, please speak with your study 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 COBI and darunavir in combination with other HIV medications.

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 and within 30 days of last dose of study drug, 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. The study doctor will request to track your pregnancy and will report the pregnancy and outcome to Gilead. Information on any problems or complications during your pregnancy and your delivery will be recorded. In addition, health information about your baby such as weight, APGAR scores and condition will be reported.

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 have treatment for your HIV infection 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 that may affect your willingness to participate in this study.

STATEMENT ABOUT PRIVACY

Records identifying you will be kept confidential and, to the extent permitted by applicable laws and/or regulations, will not be made publicly available. In the event of any publication regarding this study, your identity will remain confidential.

Representatives from government agencies, including the U.S. Food and Drug Administration ("FDA"), institutional review boards, the Sponsor and/or the Sponsor's authorized representatives may need access to your original medical records and study records for the purpose of checking data collected for the study. By signing this consent form, you authorize this access.

Your coded study information and samples may also be used for additional unanticipated medical and/or scientific research projects in the future relating to HIV-1 or the development of COBI and/or darunavir). All samples stored for the study will have a code number on them, no information such as name, birthdate, medical record number will be on the tube.

By signing this consent form you agree that you will not be able to have access to information about your participation in the study until the study is over. After that, you can obtain access to your information through your Study Doctor.

AUTHORIZATION TO USE AND DISCLOSE RECORDS

The authorization part of the consent gives more detailed information about how your personal health information may be used and disclosed by the University of Pennsylvania Health System (UPHS), the School of Medicine and the individual Principal Investigator, subject to University of Pennsylvania procedures.

What personal health information is collected and used in this study and might also be disclosed?

The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

- Name, address, telephone number, date of birth
- Social Security Number (if you receive more than $600 for participating in studies at PENN, we will need your SSN for the W-9)
- Personal and family medical history
- Current and past medications or therapies
- Results of physical exams, laboratory tests and procedures you will undergo during this research study

Why is your personal contact and health information being used?

Your personal contact information is important for the research team to contact you during the study. Your personal health information and results of tests and procedures are being collected as part of this research study. In some situations, your personal health information might be used to help guide your medical treatment.

Which of our personnel may use or disclose your personal health information?

The following individuals may use or disclose your personal health information for this research study:

- The Principal Investigator and the Investigator's study team
- Authorized members of the workforce of the UPHS and the School of Medicine, and University of Pennsylvania support offices, who may need to access your information in the performance of their duties (for example: for research oversight and monitoring, to provide treatment, to manage accounting or billing matters, etc.).

Who, outside of UPHS and the School of Medicine, might receive your personal health information?
As part of the study, the Principal Investigator, the study team and others listed above, may disclose your personal health information, including the results of the research study tests and procedures. This information may be disclosed to those listed below:

Individuals or organizations responsible for administering the study:

- Pharmaceutical sponsor (Gilead Sciences): This is the company that supplies drugs for the study. Information regarding safety and adverse effects needs to be collected and monitored.
- Contract Research Organization: Monitors will visit the site on a regular basis to review data and assure accuracy and completeness of information before the data are analyzed.

Regulatory and safety oversight organizations

- The Food and Drug Administration and regulatory agencies in other countries
- The Office of Human Research Protections
- The Study Monitoring Committee

Once your personal health information is disclosed to others outside of UPHS or the School of Medicine, it may no longer be covered by federal privacy protection regulations. Data are reported to the sponsor on Case Report Forms that identify you by your unique study number and not your name or medical record number. Information regarding your health, such as side effects of the study medications you experience will be reported only by code number. All samples collected for analysis will be labeled with your study number, visit number and date of your visit.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may UPHS and the School of Medicine be able to use or disclose your personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research repository (database). However, UPHS and the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization to do so
- The University of Pennsylvania's Institutional Review Board grants permission after ensuring that appropriate privacy safeguards are in place
- As permitted by law

Will you be able to access your records?

During your participation in this study, you might not be able to access some or all of your medical records. For example, access to portions of your medical records may be denied in studies where your knowledge of study results included in such records could affect the reliability of the study. You will have access to your medical record information when the study is over or earlier, if possible. The Principal Investigator is not required to release research information to you that is not part of your medical record.

Can you change your mind?
Yes, at any time you may withdraw your approval to allow the use and disclosure of your personal health information as described here. You must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission to use your personal health information, you will also be withdrawn from the research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study. You will also be given the UPHS and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your personal health information.

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), or (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 learned 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

COBI, darunavir, and emtricitabine/tenofovir used in this study will be provided to you free of charge for the duration of the trial. You will be reimbursed for any costs if you are prescribed other NRTIs. All clinic, professional, diagnostic, and laboratory fees for tests and procedures that are part of this study will be provided at no cost to you. You or your usual health care payer will be responsible for any other health care costs.

PAYMENT FOR PARTICIPATION

You will be paid $25.00 for your screening visit. For visits thereafter, Baseline, 8 visits through week 48 and a 30 day follow up visit you will be paid $50 for every visit you attend. Thus if you attend all required visits for the study, the maximum payment you can receive is $525. If you need to come in for

an unscheduled visit that is requested by the study staff, you also will be paid $10 for that visit. If you participate in the rollover extension, you will continue to be paid $50 for each visit until the study is over.

Please note that if you receive more than $600.00 compensation in one year for participation in research studies at the University of Pennsylvania, you must provide an Individual Tax Identification Number or Social Security Number for tax purposes.

COMPENSATION FOR STUDY-RELATED INJURY

If you are injured or become sick as a direct result of taking the study drug and/or following the study procedures, University of Pennsylvania will provide you with medical treatment. The Sponsor, Gilead Sciences, Inc., will reimburse you or the University of Pennsylvania for the reasonable and necessary costs of such medical treatment. No other form of reimbursement for study-related injury or illness is offered by the Sponsor. You do not give up any legal rights by signing this form. You should immediately contact your Study Doctor at the contact information shown on the first page of this form in the event you experience any study-related illness or injury.

If you receive Medicare benefits, the Sponsor, Gilead Sciences, Inc., is required by law to report payments made to you for treatment, complications, and injuries that arise from this Study. Information that you are taking part in the Study, medical treatments received, Medicare claims, and other personal information about you such as your name, social security number, and date of birth, will be provided to the Centers of Medicare and Medicaid Services and its agents and/or contractors for this purpose.

SOURCE FOR ADDITIONAL 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

CLINICALTRIALS.GOV REGISTRY

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

AGREEMENT TO BE IN THE STUDY

This Subject Information and Informed 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 a checkmark **(X)** 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
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
7. Do you agree to have your personal information collected during this study and blood and urine samples stored for future commercial research related to the treatment, prevention or diagnosis of HIV-1?	___ Yes ___ No
8. Do you understand that you will not have any rights to any discovery or inventions which result from future research, and you will not receive any financial compensation in connection with any future research?	___ Yes ___ No

If you answered NO to any of the eight 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.

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.

STATEMENT OF CONSENT

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____ ____/____/____
Signature of Research Subject Date

_____
Printed Name of Research Subject

STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject the nature and purpose of the above study. There has been an opportunity for the subject to ask questions about this research study. I have been available to answer any questions that the subject has about this study.

_____ ____/____/____
Signature of Person Explaining Consent Date

_____
Printed Name and Title of Person Explaining Consent