HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

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

Protocol Title:	**A5346, Version 1.0, 06/22/15**: A Randomized, Double-Blinded, Placebo-Controlled Trial of a Dipeptidyl Peptidase-4 Inhibitor (Sitagliptin, Januvia) for Reducing Inflammation and Immune Activation in HIV-Infected Men and Women A DIVISION OF AIDS/ AIDS CLINICAL TRIALS GROUP (ACTG) Study
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24 hr. Emergency Contact:	Immunodeficiency Program Doctor on call (215) 662-6059

Introduction:

You are being asked to take part in this research study because you are infected with HIV and are doing well on your medications. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: Dr. Pablo Tebas. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

Why Is This Study Being Done?

Since HIV-infected people started taking HIV medications, illness from AIDS has decreased, but other serious diseases like heart disease, cancer, and kidney and liver disease have increased. HIV causes inflammation (irritation) inside the body that cannot be felt but can be measured by blood tests. Inflammation can lead to diseases that have become some of the leading causes of death in people with HIV. HIV therapy can partially lower levels of inflammation measured in blood, however, levels of inflammation in people who have HIV may remain high compared with those found in people not infected with HIV, even when the virus is well controlled.

The purpose of the study that you are being asked to take part in is to evaluate whether sitagliptin (Januvia is the brand name for sitagliptin) reduces inflammation and immune activation markers in HIV-infected men and women when compared to a placebo (inactive medication like a dummy pill). The study will evaluate whether taking 100 mg of sitagliptin by mouth daily for 16 weeks is safe and effective for HIV-infected persons on antiretroviral therapy (ART). Sitagliptin is a medication that is used to treat people with diabetes (high blood sugar) but also may reduce inflammation in the body.

How Many People Will Take Part in This Study?
About 86 people will take part in this study. About 5 people are expected to enroll at the University of Pennsylvania.

How Long Will I Be In This Study?
You will be in this study for about 20 weeks

What Do I Have To Do If I Am In This Study?
If you agree to join this study, you will be asked to sign this consent form. Before signing it, ask your study nurse or doctor to explain anything that you do not fully understand. After you have signed the form, you will be asked some questions and will undergo some tests to see if it is safe for you to join the study (these visits are called the screening visits).

The evaluations performed at the screening visits are listed in Table 1 of this informed consent.

You will receive the results of the HIV viral loads, the routine safety blood tests, and the pregnancy test.

If you do not enroll into the study
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, viral load) information is being collected from you so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study. If you do not want your information to be used, then you should not sign this consent form.

You will be required to come to most visits fasting;
- Fasting means that you should not eat or drink anything for at least 8 hours before your visit.
- You may drink only water and take your prescription medications during this time.
- The study staff will remind you about fasting before study visits.

Pre-entry
If your blood tests show that you have met all of the requirements to enter the study and you choose to participate in the study, you will come to the clinic at least 24 hours after the screening visit to complete the pre-entry evaluations before study entry. The evaluations listed in Table 1 of this informed consent will also be performed during this visit.

Entry
If you have met all of the requirements to enter the study you will come to the clinic at least 24 hours after the pre-entry evaluations for the entry evaluations. The evaluations listed in Table 1 will also be performed.

At this visit, you will begin taking the provided study drug (sitagliptin) or placebo (dummy pill). You will be randomized into the study by chance (like the flip of a coin) to one of two treatment arms:

Group 1: Sitagliptin 100 mg daily for 16 weeks, followed by a 4-week post-intervention follow-up.

Group 2: Placebo for sitagliptin 100 mg daily for 16 weeks, followed by 4-week post-intervention follow-up.

This is a double-blind study, which means neither you nor the study staff will know which treatment group you are in.

The study drug sitagliptin and placebo are provided by the study and will be given to you at this visit. Your other HIV medications will not be provided by the study; you will need to continue to obtain them through your HIV care doctor or provider.

It is very important that you continue taking all of your regular anti-HIV medications as well as the study medicine. If you miss doses of the anti-HIV medicines, your virus may become resistant to the medicines, which means that the treatment may no longer work to control your HIV. In addition, you may have to stop taking the study drug.

On-study Evaluations after Entry
You will be asked to come to the clinic 5 times in 20 weeks at weeks 4, 8, 15, 16, and 20. The evaluations performed during these visits are listed in Table 1 of this informed consent.

If you stop taking the study medication before the last week of the study treatment, you will be asked to come into the clinic and have a physical exam performed, have blood collected, and answer questions about how you take your medications.

If you stop taking part in the study before the end of the study, you will be asked to come into the clinic and have a physical exam performed, have blood collected, and answer questions about how you take your medications.

Virologic Failure
If, at any point during the study, you are found to have an HIV viral load value that is higher than expected (more than 200), you will be asked to come back in for another viral load test to make sure the first one was correct. If your second viral load is still more than 200, your study doctor will take you off the study drug or placebo and you will discontinue the study. You will be asked to complete the discontinuation evaluations.

Use of Your Samples for this Study
Some of your blood samples will be stored and used for testing that is required for this study. No one will know just from looking at the labels of your stored samples that they came from you.

Use of Your Stored Samples
If you agree, some of your blood , urine, and stool samples that are left over after all required study testing is done may be stored for future research that is not yet planned, including future ACTG-approved HIV-related. No one will know just from looking at the labels of your stored samples that they came from you. Although researchers will not be given your name or any other personally identifying information about you, some information about your medical condition, your race, ethnicity, gender, and age may be shared.

These samples will be kept frozen for an indefinite length of time. We cannot ensure that you will be told of the results of the research done on these samples.

Allowing your samples to be stored for this use is optional. You will be asked to confirm whether or not you allow your samples for later use at the end of this consent form. No matter what you decide, it will not affect your participation in the study.

If you decide now that your samples can be stored for research to be done at a later date, you may change your mind at any time. If you change your mind, you must contact your study doctor or nurse and let them know that you do not want your samples used for research to be done at a later date. Every effort will then be made to destroy your left-over samples.

Table1. Evaluations performed during the study

Evaluation or Test	Screening	Pre-Entry	Entry	Post Entry Visits					Early Discontinuation
				W4	W8	W15	W16	W20	
Consent	✓								
Physical exam	✓		✓	✓	✓	✓	✓	✓	✓
Fasting blood and/or urine collected	✓	✓	✓		✓	✓	✓	✓	✓
Blood draw (mls)	*28*	*70*	*95*	*0*	*79*	*103*	*60*	*70*	*13*
Tablespoons	*2*	*5*	*6*	*0*	*5*	*7*	*4*	*5*	*1*
Stool swab			✓			✓			
Adherence assessments				✓	✓		✓		✓
Pill Counts				✓	✓		✓		✓

Description of Evaluations

Complete Physical Exam

- You will be asked about any new medical issues or symptoms that have occurred since your last study visit, especially possible side effects to the medicine you are taking.
- Your height, weight, temperature, blood pressure, pulse, and breathing rate will be measured.
- You will be asked about any changes in the type or amount of medication or nutritional supplements (prescription and over the counter) you have been taking.

Targeted Physical Exam

- You will be asked about any new medical issues or symptoms that have occurred since your last study visit, especially possible side effects to the medicine you are taking.
- Your temperature, blood pressure, pulse, and breathing rate will be measured.
- You will be asked about any changes in the type or amount of medication or nutritional supplements (prescription and over the counter) you have been taking.

Blood and/or Urine Tests

- Safety Blood Tests
  - Routine tests of your liver, your kidneys, and your blood counts
  - You will be given the results of this test as soon as they become available.

- Pregnancy Test
  - If you are a woman able to become pregnant, you will have a urine or blood test at screening, entry, and whenever pregnancy is suspected to make sure that you are not pregnant.
  - You will be given the results of this test as soon as they become available.
- CD4+/CD8+ T-cell Count
  - This is a measure of your immune system; T-cells help the immune system fight infections.
  - You will be given the results of these blood tests as soon as they become available.
- HIV-1 RNA (Viral Load)
  - This measures the amount of HIV in your blood.
  - You will be given the results of this test as soon as they become available.
- Blood and Urine Tests for Immunology Assays and Virologic Studies
  - These blood samples will be used to measure inflammation inside your body and to check your T-cells for how well they are working.
  - Your blood will be stored and will be tested after the study is over. You will not be given the results.

Stool Swab Test
- A stool swab to study the different kinds of bacteria in your stool will be self-collected, frozen and stored for possible testing after the study is over. You will not be given the results.

Adherence Assessments
- You will be asked about how well you take your study-provided medications. The study staff will give you information and encouragement to help you take your medications as prescribed.
- If you miss doses of your HIV medications or stop taking them for any reason, please tell the study staff.

Pill Count
- You will be asked to bring in the pill bottles that you have been given with all pills that remain (including any that you may have missed or have not yet taken).
- The study staff will count the number of pills.

Why Would The Doctor Take Me Off This Study Early?

The study doctor may need to take you off the study early without your permission if:
- the study is stopped or cancelled
- you experience virologic failure
- you are not able to attend the study visits as required by the study
- if requested by your primary care provider
- if you are judged by the investigator to be at significant risk of non-compliance

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

- continuing the study drug(s) may be harmful to you
- you need a treatment that you may not take while on the study
- you are not able to take the study drug(s) as required by the study
- you become pregnant

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

If I have to permanently stop taking study-provided sitagliptin (Januvia) or once I leave the study, how would sitagliptin (Januvia) be provided?

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

After the study:
After you have completed your study participation, the study will not be able to continue to provide you with sitagliptin you received on the study.

What Are The Risks Of The Study?
The study drug used in this study may have side effects, some of which are listed below. Please note that this list does not include all the side effects seen with this drug. This list includes the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

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

- Pancreatitis (inflammation of the pancreas), which may cause death. Certain medical problems make you more likely to get pancreatitis:
  - stones in your gallbladder (gallstones)
  - high blood triglyceride (a common type of fat) levels
    Stop taking sitagliptin and contact your healthcare provider right away if you have pain in your stomach area that is severe and will not go away. The pain may be felt going from your stomach area (abdomen) through to your back. The pain may happen with or without vomiting, or nausea.

- Low blood sugar (hypoglycemia). Signs and symptoms of low blood sugar may include:
  - Headache
  - Drowsiness
  - Weakness
  - Dizziness
  - Confusion
  - Irritability
  - Hunger
  - Fast heart beat
  - Sweating
  - Feeling jittery

- Serious and life-threatening rash and allergic reactions. Symptoms of a serious allergic reaction to sitagliptin may include:
  - Rash
  - Raised red patches on your skin (hives)
  - Swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.

If you have any symptoms of a serious allergic reaction, stop taking sitagliptin and contact your healthcare provider right away.

- Kidney problems, sometimes requiring treatment to do the work that your kidneys can no longer do such as dialysis.

- Heart failure, which can cause difficulty breathing and swelling of the ankles.

Additional side effects include:
- Nausea/vomiting
- Stomach pain
- Diarrhea
- Back pain
- Infection of the nose, throat, or sinus
- Headache
- Hives
- Rash
- Skin Infection

Risks of Blood Draws
A needle will be used to take blood from a vein in your arm. This may lead to brief pain from the needle stick, bruising, and rarely, infection. Some people may become light-headed. The risk of taking blood includes low red blood counts, which can make you feel tired, weak, and dizzy.

Risks of Rectal Swab
You may have mild discomfort when the swab is performed, particularly if you are already suffering from sores or hemorrhoids. If you are already having pain in the rectal area, be sure to let the study team know.

Risks of Social Harm
Although the study site will make every effort to protect your privacy and confidentiality, it is possible that your involvement in the study as a participant could become known to others if it is not already and that social harms may result (because you could become labeled as being infected with HIV). For example, you could be treated unfairly or discriminated against by family members, friends, and/or the community.

Are There Risks Related To Pregnancy?
If you are a woman having sex that could lead to pregnancy, you must agree not to become pregnant. At least one of the following methods MUST be used:
- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormone-based contraceptive

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in women taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

Are There Benefits to Taking Part in This Study?
If you take part in this study, you should expect no direct benefit. Information learned from this study may help others who have HIV.

What Other Choices Do I Have Besides This Study?
Instead of being in this study you have the choice of:

- treatment with experimental drugs, if you qualify
- no treatment

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

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

People who may review your records include the ACTG, Office for Human Research Protections (OHRP) or other government agencies as part of their duties, the University of Pennsylvania institutional review board (IRB), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, other government agencies and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

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

Your records may be reviewed by the ACTG, OHRP, University of Pennsylvania IRB, National Institutes of Health (NIH), study staff, study monitors, and the drug company supporting this study.

A description of this clinical trial will be available on www.ClinicalTrials.gov. 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.

Your personal information may be given out if required by law. If you test positive for HIV or if a CD4 or HIV viral load is done at a study visit, by law we have to report the result to the City of Philadelphia Health Department/PA Department of Health. We would report your name, gender, racial/ethnic background, and the month and year you were born. This is to keep track of how many people in the U.S. have HIV infection. It is also to make sure that states get enough money from the federal government to support the medical care of people living with HIV. The Health Department does not share the names of HIV infected people with anyone else. It removes all personal identifiers, such as your name, before giving information on the number of HIV infections to the federal government.

HIPAA AUTHORIZATION
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, email address
- Dates directly related to you such as date of birth and clinic visits.
- Personal and family medical history
- Current and past medications or therapies
- Questionnaires
- Results of tests and procedures you will undergo during this research
- Social Security Number, Medical record number

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:

- ACTG Data Coordinating Center, Frontier Science Technology Research Foundation (FSTRF): Data for this study will be recorded on case report forms, keyed into a central database and electronically submitted to the Data Coordinating Center. The data will be cleaned and stored at this facility until it is ready to be analyzed.
- Statistical Data Analysis Center (SDAC): Approved data will be downloaded from FSTRF to the statistical data center for the AACTG at the Harvard School of Public Health. Specific study reports will be periodically provided to the study team and data safety review board to monitor if the trial is safe.
- Pharmaceutical sponsor (Merck) The company that is supplying the study drugs.
- Contract Research Organization (PPD, Inc): Monitors from PPD will visit the AACTG on a quarterly basis to review data and correct mistakes before the data are sent to SDAC for analysis.

- Government Agencies: Data from this study will be made available to the National Institutes of Health/Division of AIDS (DAIDS)/National Institute for Allergy and Infectious Disease (NIAID), for them to evaluate the safety and efficacy of the treatments being used in this study.

Regulatory and safety oversight organizations

- The Office of Human Research Protections

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, date of birth or medical record number. Information regarding your health, such as side effects of the study drug 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 database. However, 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
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?
Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You must do so in writing to the Principal Investigator at Infectious Disease Division, 502 Johnson Pavilion Philadelphia PA 19104. 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, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this 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.

What is an Electronic Medical Record?
An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study,

results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

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

What Are the Costs To Me?

There will be no cost to you for any of the laboratory tests that you have as part of this study, study visits or Sitagliptin (drug supplied by the study). You are still responsible for any deductibles or applicable co-pays for routine office visits, procedures and blood work. Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are taking part in a research study. If you have any concerns about this, please discuss your concerns with the research staff.

Will I Receive Any Payment?

You will be compensated $50 for each required study visit (8) you attend. Compensation will be provided as cash. The total compensation for the study is $400 if all required visits are attended. If you are requested by the study team to come in for an unscheduled visit, you will be compensated $25 for that visit.

There is no other form of compensation available such as reimbursements for parking, tokens or child care. In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

What Happens If I Am Injured?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania or the National Institutes of Health to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

What Are My Rights As a Research Subject?

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

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

What Do I Do If I Have Questions Or Problems?

If you have questions about this study or a research-related injury, please contact the research team listed on page 1 of this consent form.

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

On page 4 of this consent form you were informed about optional tests to be done on your leftover blood.

Please indicate below "yes" or "no" and initial and date whether you approve the use of these extra stored samples for future testing. Note that you can withdraw your consent for research on stored specimens at any time you want and the specimens will be discarded. Your refusal or withdrawal of consent for the storage of these samples will not affect your study participation since storage of leftover samples is not a requirement for the study.

☐ I agree to allow additional testing performed my extra samples for future ACTG-approved research

☐ I do not allow my extra samples to be used in future research

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you. You will also be given the University of Pennsylvania Health System and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your health information.

Name of Subject (Please Print)	Signature of Subject	Date/Time
Name of Person Obtaining Consent (Please Print)	Signature	Date/Time