UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

A5240, Version 2.0, 10/6/10
A Phase II Study to Evaluate the Immunogenicity and Safety of a Quadrivalent Human Papillomavirus Vaccine in HIV-1-Infected Females

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

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

Principal Investigator: Ian Frank, MD (215) 662-7419
Coordinator: Joseph Quinn, RN (215) 349-8092
Study Nurse: Aleshia Thomas, RN (215) 349-8092

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

Introduction:
You are being asked to take part in this research study because you are infected with HIV (the virus that causes AIDS). This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is Dr. Ian Frank. Before you decide if you want to be a part of this study, we want you to know about the study.

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

Why Is This Study Being Done?
Human papillomavirus (HPV) is a DNA virus. HPV infection is the most common sexually transmitted disease (STD) in the United States and worldwide. There are over 90 types of HPV that infect humans. Some of these types infect the genital and anal areas where the infection causes genital and anal warts. It also causes cancer of the cervix (opening of the uterus) in females. Merck & Co., Inc. makes a quadrivalent HPV vaccine, called GARDASIL. “Quadrivalent” means that this vaccine is directed at four types of HPV. This vaccine does not protect you against other types of HPV, other STDs, or HIV. This vaccine has been approved by the U.S. Food and Drug Administration (FDA) for use in females 9 to 26 years of age.

HPV infection can be more severe and harder to treat in people infected with HIV. This study will see if the HPV vaccine, when given in 3 separate doses, is safe and tolerable in females infected with HIV. This will be done by asking how you feel and if you had any reactions after each dose of the vaccine. The study will also look at if the HPV vaccine can help the body make substances in response to the vaccination to help fight off disease. This is the first time GARDASIL is being tested in females infected with HIV.

Since the vaccine is made with parts that are like the HPV virus but not the virus itself, it cannot cause the HPV disease.

What Do I Have To Do If I Am In This Study?
The vaccine will be provided to you by the study. If you are currently taking anti-HIV drugs, you can continue taking them. Your anti-HIV drugs will not be provided to you by the study. You must get them through your primary care provider.
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Before the Study Starts
After you have read and signed this informed consent form, you will come to the clinic for a screening visit to make sure you meet the requirements for joining the study. The screening visit should last about 1 hour, but it may be shorter or longer. The screening visit will include:

- A confirmation of your HIV infection. If there is no record available, another HIV test will be required. You may have to sign a separate consent form before this is done.
- A complete physical exam. You will also be asked to answer questions about your medical history and medications you are taking now and have taken in the past.
- About 3 teaspoons of blood will be taken from a vein for routine safety tests and CD4+/CD8+ cell counts (the number of white blood cells that fight infection).
- If you are able to become pregnant, you will have a pregnancy test done (blood or urine); about 1 teaspoon of blood will be taken from a vein or you will give a urine sample in the clinic for the pregnancy test. You will not be able to enroll in this study if you are pregnant or breast-feeding.
- A Pap test will be done at this time if you have not had one in the past 6 months. A Pap test is the collection of a very small amount of cells obtained by a gentle scraping of the cervix (the opening to the womb or uterus).

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 the screening visit, some demographics (e.g., age, gender, race), clinical information (e.g., disease condition, diagnosis), and laboratory information (e.g., CD4 cell count) 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.

Study Entry
If you qualify for the study, you will return to the clinic within the next 45 days after the screening visit.

The study entry visit should last about 1 hour, but it may be shorter or longer. The study entry visit will include:

- A brief physical exam. You will also be asked to answer questions about medications you are taking now and have taken in the past. You will be asked a question about your lowest ever CD4+ cell count.
- A brief oral exam to check if you have HPV in your mouth. This involves looking at your tongue, cheeks, roof of mouth, floor of mouth, lips and gums.
- You will be asked about any recent signs/symptoms since the screening visit.
- About 4 teaspoons of blood will be taken from a vein for routine safety tests. You will have an HIV viral load test (a measure of how much HIV is in your blood) and a CD4+/CD8+ cell count.
- About 2 teaspoons of blood will be taken from a vein for an HPV antibody test. HPV antibodies are cells in the blood that fight the HPV virus. You will not be told the result of this test because it will be done in the future.
- If you are able to become pregnant, you will have a pregnancy test done (blood or urine); about 1 teaspoon of blood will be taken from a vein or you will give a urine sample in the clinic for the pregnancy test. This test may not be needed if you had a negative pregnancy test within 2 days before the study entry visit.
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- The level of HIV viral load in the cervix will be measured by inserting a speculum (an instrument that stretches the opening of the vagina) into the vagina and then inserting 2 filter papers (TearFlo) inside the cervical canal (opening of the cervix) for about one minute. You will not be told the result of this test since it will be done in the future.
- A cervical brush and an anal swab will be performed for future HPV DNA testing. This is a test to determine the types of HPV found in your cells. A doctor or nurse will insert a small brush into your cervix and a swab into your anus. You will not be told the results of these tests since they will be done in the future.

It is required that you do not have any sexual activity and that you do not douche or use any anal/vaginal products in or around your anus/vagina for at least 48 hours before the following tests: the collection of fluid from the cervix using filter paper (TearFlo), the cervical brush, and the anal swab.

You will be told the results of the following tests as soon as this information becomes available: routine safety tests, HIV viral load test, CD4+/CD8+ cell counts, and pregnancy test.

After the study entry evaluations, you will receive the HPV vaccine (GARDASIL) by intramuscular injection (an injection into the upper arm muscle or thigh). After you receive the vaccine, you will remain in the clinic for at least 30 minutes (½ hour), so that clinic staff can observe you to make sure that you do not develop a bad reaction from the vaccine. Within a day or two of having received the vaccine, you must be available for a telephone call or a visit by the clinical staff to answer short questions about how you feel and any reactions you may have had. The study staff may ask you to come to the clinic if you are having any bad reactions from the vaccine.

During the Study
You will return to the clinic for a visit at weeks 4, 8, 12, 24, 28, 52, and 72. We think each visit during the study will take about 1 hour but may be shorter or longer. At each of these visits:
- About 1 teaspoon of blood will be taken from a vein to determine your CD4+/CD8+ cell count.
- You will have a brief physical exam. You will also be asked to answer questions about medications you are taking now and have taken in the past.
- You will be asked about any recent signs/symptoms since your last visit.
- Before each vaccine and at any time you think you may be pregnant, you will have a pregnancy test done (blood or urine); about 1 teaspoon of blood will be taken from a vein or you will give a urine sample in the clinic for the pregnancy test.

You will receive the HPV vaccine (GARDASIL) by intramuscular injection again at weeks 8 and 24. After you receive the vaccine, you will remain in the clinic for at least 30 minutes (1/2 hour), so that clinic staff can observe you to make sure that you do not develop a bad reaction from the vaccine. Within a day or two of having received the vaccine, you must be available for a telephone call or a visit by the clinical staff to answer short questions about how you feel and any reactions you may have had. The clinic staff may ask you to come to the clinic if you are having any bad reactions from the vaccine.

Most study visits will also include:
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- A brief oral exam.
- About 2 teaspoons of blood taken from a vein for HPV antibody testing. You will not be told the result of this test because it will be done in the future.
- About half (1/2) a teaspoon of blood taken from a vein to determine your HIV viral load.

Study visits at weeks 4, 12, and 28 will also include:
- About 1 tablespoon of blood taken from a vein for routine safety tests.

Study visits at weeks 28 and 52 will also include the following. You will not be told the results of these tests because they will be done in the future.
- The level of HIV viral load measured in the cervix by filter paper (TearFlo) for future testing.
- Cervical brush and anal swab performed for future HPV DNA testing.

The study visit at week 52 will also include:
- A complete physical exam.
- A Pap test.

It is required that you do not have any sexual activity and that you do not douche or use any anal/vaginal products in or around your anus/vagina for at least 48 hours before the following tests: the collection of fluid from the cervix using filter paper (TearFlo), the cervical brush, and the anal swab.

You will be told the results of the following tests as soon as this information becomes available: CD4+/CD8+ cell counts, pregnancy tests, HIV viral load, routine safety tests, and Pap test.

Extra tests only for a subset of participants in the U.S.A. enrolled under protocol version 1.0:
You may have been one of 75 study participants who already agreed under protocol version 1.0 to have extra tests. We think these extra tests will take an additional 30 minutes (1/2 hour) or less at some of the study visits.

Most study visits will include the following extra tests:
- About 3 tablespoons of blood taken from a vein for future immune response testing. This is a test for the presence of cells in the blood that fight infections.

At the study entry visit and at weeks 28, 52, and 72:
- If a wart is seen in your mouth during the brief oral exam, you will have a small smear collected by brushing the wart for future HPV DNA testing.

The study entry visit and study visits at weeks 28 and 52 will also include the following tests for future HPV DNA testing:
- Two (2) small smears collected by brushing the back of your tongue and cheek.
- You will gargle saltwater and then spit in a tube.
- You will then sit for a minute without swallowing and then spit into a tube again.
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The fluids collected from your mouth and your blood sample will be stored with usual protectors of identity and used for future testing that is required for this study. You will not be told the results of these extra tests because they will be done in the future.

PLEASE CHECK ONE OF THESE BOXES:

☐ I am willing to have all of these extra tests done, if I am asked.
☐ I am NOT willing to have these extra tests done.

Leftover samples:

If you agree, some of your blood and other samples collected for the study that are left over after all required study testing is done may be stored and used for future ACTG-approved HIV-related research. These left over samples will be stored with the usual protectors of identity. These left over samples may be stored for an indefinite length of time. We cannot ensure that you will be told the results of the research done on these samples.

Storage of left over samples is not necessary to participate in the study. Even if you agree now, you may withdraw your approval for the storage of your left over samples at anytime in the future. Please indicate below, by signing your initials, whether you approve the use of your left over samples.

_____YES _____NO

Premature Study Discontinuation

If you wish to leave the study, you will be asked to come to the clinic for a final study visit. This visit will include most of the evaluations listed under “Study Entry,” plus a Pap test. You will be told the results of the following tests as soon as this information becomes available: HIV viral load, CD4+/CD8+ cell counts, and Pap test.

Permanent Study Treatment Discontinuation

If you permanently stop receiving the vaccine before the last required dose at week 24, you will be asked to still come to the clinic for all the remaining study visits.

How Many People Will Take Part in This Study?

About 282 women will take part in this study. About 10-15 women are expected to participate at the University of Pennsylvania.

How Long Will I Be in This Study?

You will be in this study for about one and a half (1 ½) years.

Why Would the Doctor Take Me Off This Study Early?

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

- the study is cancelled by the U.S. Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), other government agencies, the ACTG, the drug company supporting this study, or the site’s Institutional Review Board.
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Board (IRB), Ethics Committee (EC), or other country-specific review board. (An IRB or EC is a committee that watches over the safety and rights of research participants.)

- a Study Monitoring Committee (SMC) recommends that the study be stopped early (A SMC is an outside group of experts who monitor the study.)
- you are not able to attend the study visits as required by the study
- your doctor no longer thinks participating in the study is in your best interest
- you did not receive the vaccine as required by the study

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

- continuing the study vaccine may be harmful to you
- you need a treatment that you may not take while on the study
- you become pregnant or begin breast-feeding
- you are not able to keep with the vaccine schedule as required by the study

If you must stop having the study vaccine before the study is over, the study doctor may ask you to continue to be part of the study and return for all study visits and procedures.

If I have to permanently stop having study-provided vaccines or once I leave the study, how would the vaccine be provided?

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

What Are The Risks Of The Study?
The vaccine 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 this vaccine. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional vaccine side effects, please ask the medical staff at your site.

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 risks of the study vaccine (GARDASIL) are listed below.
The following serious side effects have been associated with the use of gardasil:

- Hypersensitivity (allergic) reactions, such as rash, fever, flu-like feeling, blisters, facial swelling, or even problems breathing. These reactions, in severe form, may be life threatening.
- Guillain-Barré Syndrome (a form of paralysis)

In addition to the serious side effects listed above, additional side effects may include
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- Soreness, tenderness, itching, redness, bruising or swelling at the injection site
- headache
- fever
- Nausea and vomiting
- Dizziness
- Fainting may occur after receiving the injection, which may result in falling with injury. Shaking, stiffening and other seizure-like activity have also been reported.
- Tiredness
- Chills

The risks of study procedures are listed below.

Blood drawing
Taking blood may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting or infection.

Pap test, oral smears, cervical brush, and anal swab
These tests can be uncomfortable. Occasionally there can be some bleeding, a tingling feeling, or slight stinging.

Oral exam
The oral exam can be uncomfortable, but should be painless.

Are There Risks Related To Pregnancy?
If you become pregnant during the study, you will not receive any more vaccinations. If you decide to stay in the study, you will be asked to sign a pregnancy informed consent form. If you give consent, you will continue to have most of the study tests. There are 4 study tests that you will not have:
- The level of HIV viral load measured in the cervix by filter paper (TearFlo) for future HIV testing
- Cervical brush and anal swab for future HPV testing
- Pap test

Also, study staff will contact you to ask you about the outcome of the pregnancy.

The vaccine in this study may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant.

Because of the risk involved, you and your partner must use at least one method of birth control that you discuss with the study staff. You must continue to use at least one method until 48 weeks (close to 1 year) after the last vaccination. You may choose one or more of the birth control methods listed below:
- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- IUD
- Hormone-based contraception

If you are taking certain anti-HIV drugs (Efavirenz), you and your partner must use at least two of these methods of birth control. The study staff will discuss this with you.
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If you can become pregnant, you must have a pregnancy test before you enter this study and before each vaccination. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices.

Are There Benefits to Taking Part in This Study?
If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

What Other Choices Do I Have Besides This Study?
Instead of being in this study, you have the choice of:
- Receiving the HPV vaccine (GARDASIL) from your doctor
- Not participating in this study at all
- Participating in another study, if you qualify

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 U.S. Food and Drug Administration, University of Pennsylvania IRB, the National Institutes of Health, the Office for Human Research Protections, the ACTG, study staff, study monitors, drug company supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

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

What Are the Costs To Me?
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.

Will I Receive Any Payment?
You will be compensated $25 for each clinic visit you attend with the exception of the screening visit to cover transportation costs, parking, child care, etc and for your time and inconvenience. At the screening visit, if you need a PAP test, you will be compensated $50 for your inconvenience. You will be compensated an additional $50 (i.e. a total of $75 for the visit) at Entry, week 28, week 52 and premature discontinuation when PAP and or cervical cytobrush/anal swab samples are
obtained. Thus, if you attend all study visits, the maximum compensation you will receive from the study is $350. 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. In addition, if you are one of the 75 participants that agrees to participate in the oral specimen collection as described in the “Other” section of this consent, you will be compensated an additional $20 at each of the visits when this is required (entry, wk 28, wk52, premature discontinuation). Thus, at these visits the maximum compensation you will receive is $95.

**What Happens If I Am Injured?**
If you have a medical emergency during the study you should go to the nearest emergency room. You may contact the Principal Investigator or Emergency contact listed on page one of this form. You may also contact your own doctor, or seek treatment outside of the University of Pennsylvania. Be sure to tell the doctor or his/her staff that you are in a research study being conducted at the University of Pennsylvania. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

In the event that you are hurt or injured as a result of participation in this research study, please contact the investigator listed on page one of this form.

In the event of any physical injury resulting from research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise offered from the University of Pennsylvania or the National Institutes of Health. If you have an illness or injury during this research trial that is not directly related to your participation in this study, you and/or your insurance will be responsible for the cost of the medical care of that illness or injury.

**What Are My Rights As a Research Subject?**
Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your healthcare provider will treat you the same no matter what you decide.

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

**What Do I Do If I Have Questions Or Problems?**
For questions about this study or a research-related injury, contact:
- Pablo Tebas, MD (215-615-4321)
- 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
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.

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For subjects unable to give authorization, the authorization is given by the following authorized subject representative:

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Provide a brief description of above person authority to serve as the subject’s authorized representative.