INSTITUTE: National Cancer Institute

STUDY NUMBER: 09-C-0024 PRINCIPAL INVESTIGATOR: Lauren V. Wood, M.D.

STUDY TITLE: A Phase I Study of Quadrivalent Human Papilloma Virus (HPV) (Types 6, 11, 16, 18) Recombinant Vaccine in HIV-Infected and HIV-Negative Pre-Adolescents, Adolescents and Young Adults

Continuing Review Approved by the IRB on 07/26/10
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INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Description of Research Study

This is a study of a recently approved vaccine for Human Papilloma Virus (HPV). This vaccine induces immunity to four types of HPV- HPV 6, 11, 16 and 18. It was shown to be highly effective in preventing infection with these HPV types and was approved by the FDA in June 2006 for use in females 9 to 26 years of age. In October of 2009 it was approved for prevetion of genital warts in boys and men ages 9-26 and in December of 2010 the vaccine was approved for prevention of anal cancer and precancerous AIN 1, 2, 3 in females and males ages 9-26. However much less is known about the vaccine's ability to induce immunity in males or individuals with suppressed immune systems. This study is investigating

whether the HPV vaccine is safe to give and able to induce immunity in both female and male adolescents and young adults with HIV infection compared to healthy, HIV-negative persons of the same age.

Background

HPV is a common sexually transmitted disease that is acquired soon after young people become sexually active. There are over 100 different HPV types and both males and females can get HPV infection. Most people do not have any symptoms when they become infected and are able to get rid of the infection on their own. However, they can still become re-infected with the same or a different HPV type, and in some people HPV infection persists. Persistent HPV infection is associated with the development of precancerous lesions and cancer. HPV types are classified as either high risk or low risk based on whether their persistence will lead to cancer. HPV types 16 and 18 are considered high risk as they are associated with 70% of cervical and other anogenital cancers. Types 6 and 11 are considered low risk as they are associated with warts that occur on the genitals and skin.

Patients who have suppressed immune systems are at a higher risk for HPV-related complications. They are more likely to contract multiple HPV types and have more persistent infection that can lead to precancerous lesions or cancer, which are then difficult to treat and often recur. Specifically, patients with HIV are known to have worse HPV disease and in females, cervical cancer is an AIDS defining illness.

HPV is a DNA virus that has a complex structure. The outer coat protein of the virus is called L1. It was shown in the lab that L1 proteins manufactured by recombinant DNA technology could self-assemble into viral-like particles (VLPs). These VLPs look like a virus to the immune system but are not infectious and induce immunity to HPV that protects from infection and precancerous lesions. The vaccine being studied in this protocol contains the outer coat L1 protein from 4 different HPV types: HPV 6, 11, 16 and 18. For this reason, the vaccine is known as a quadrivalent HPV VLP vaccine. Although, there is some preliminary data on the immunity of the vaccine in males it is not yet approved for routine vaccination. There is also no data on vaccine immunity in patients with HIV infection or other types of immune suppression.

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In large clinical studies involving thousands of young women, including some women who had previous exposure to HPV, the vaccine was shown to be 100% effective in preventing HPV-related precancerous lesions. The vaccine was tolerated very well and had few side effects other than local injection site reactions.

Study Procedures

Before beginning vaccination, you will be required to be evaluated in the outpatient clinic. You will be under the care of a specialist in pediatrics, infectious diseases and/or immunology. You will have a complete physical examination. Blood will be taken for routine blood tests, special tests of the immune system, antibody tests, and an HIV test. If you have any questions regarding the HIV testing you are encouraged to discuss them with your physician and/or a Clinical Center HIV counselor: (301) 496-2381. About two ounces of blood is needed for these tests. All of these tests will be performed prior to the first vaccination. If you are female and have started to have periods, a pregnancy test using a urine sample will be done before vaccination and at each follow-up visit. If any of these studies show any condition that would make it dangerous for you to participate in this study, we will advise you of the results and recommend alternatives for treatment that may be available to you. During the study we will also store some of your blood for additional HIV or HPV research tests in the future. You can choose whether you want your blood specimens to be used for possible future research studies.

As part of this study we are also determining what types of HPV individuals carry and have been exposed to. Blood tests will allow us to measure antibodies to different HPV types before you receive the vaccine. In order to determine the types of HPV individuals are carrying, we will take oral samples by rubbing a cytobrush to the inside of the cheeks. We will also do a swab of the anogenital area to allow us to directly detect HPV DNA. For the anogenital test, a physician or nurse practitioner will gently rub a soft Q-tip like swab over the external genital area. Young women who are or have been sexually active will have a routine gynecologic evaluation that includes a pap smear and HPV DNA testing prior to receiving the vaccine.

The HPV vaccine will be given by injection into the muscle at 0, 2, and 6 months (give or take 1 or 2 weeks) according to the standard vaccination schedule. You will be closely monitored for any side effects associated with the HPV vaccine and as well as for immune responses to the vaccine. After each vaccination, you will be given a vaccine report card to complete. On this report card you will record any reactions you have at the vaccine injection site such as redness, swelling, pain, tenderness or other symptoms for the 5 days after you have received the vaccine. We also want you to record your temperature and any other symptoms you have that you think may be related to the vaccine. Although it is unlikely, if unacceptable side effects (either by clinical or laboratory monitoring) develop, future vaccinations will be withheld until these side effects resolve or the vaccine will be stopped if the side effects are very severe.

This study also includes a web-based survey of health behaviors and choices that young people are commonly faced with. The survey specifically asks about activities that potentially put individuals at risk for HIV, HPV and other sexually transmitted diseases. It also contains questions that will help us determine your basic understanding and knowledge about HIV and HPV. The survey is given once at the start of the protocol and it takes about 15 to 30 minutes to complete. You may skip questions in the survey if you do not understand the question or if you feel uncomfortable answering the questions. The survey is conducted on line to protect your privacy and to ensure that the results are confidential. While the research team will have access to survey answers as a group, neither the study investigators nor your parent(s) or legal guardian(s) will be able to trace your answers back to you or have direct access to the answers you give. If you choose not to participate in the survey your participation in the study will not be compromised and you will still receive the HPV vaccine and be monitored as part of the study.

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Your first HPV vaccine injection will be given at month 0. During the first year of this study, you will come back to the clinic for 6 additional 1 day visits at months 1, 2, 3, 6, 7 (give or take up to 2 weeks) and month 12 (give or take 30 days). After the first year, you will come back twice a year (approximately every 6 months, ±30 days) for 1 day visits for 3 years. The total duration of the study is 4 years. This long-term monitoring will allow us to determine what happens to the HPV antibody levels induced by the vaccine and determine whether they decline over time.

You will be informed of any significant findings that develop during the study that may influence your condition or your willingness to continue participation.

Use of Antiretroviral Drugs in HIV-Infected Individuals

In Cohort 1 of the study individuals with HIV infection on highly active antiretroviral treatment (HAART) will receive the HPV vaccine. Individuals must be on a stable HAART regimen for 6 or more months with CD4 cell counts greater than or equal to 350 cells and HIV-1 RNA levels less than or equal to 20,000 copies/ml. The drugs used must be approved by the FDA and given in combinations that are in accordance with Public Health Service HIV treatment guidelines for adolescents and adults. You will remain on the same treatment regimen throughout the duration of the study unless you have toxicity related to your antiretroviral drugs or begin to experience symptoms that suggest your HIV treatment medications are no longer working, such as declining CD4 cell counts, increasing HIV-1 RNA levels or other clinical symptoms. If you

experience drug-related toxicity to one of your antiretroviral drugs, the dose may be modified or the drug may be replaced with other appropriate drugs during the study. If your HIV drugs no longer appear to be working, an alternate treatment regimen will be recommended in consultation with your HIV primary care provider.

Individuals with HIV infection in Cohort 2 of the study are allowed to receive the HPV vaccine alone without antiretroviral treatment because treatment is not indicated, they have elected to decline treatment, or treatment is not recommended by their health care provider because of concerns that the patient is unable to take medications consistently which may promote the development of viral resistance. If you develop any of the criteria to start antiretroviral therapy while on this study, such as declining CD4 cell counts or increasing HIV-1 RNA levels, we will begin treatment in accordance with Public Health Service HIV treatment guidelines for adolescents and adults in consultation with your HIV primary care provider.

Risks or Discomforts of Participation

The primary risks and discomforts of participating in this study are related to blood draws and injection site reactions to the vaccine. You may experience slight pain and bruising at the needle site when blood is drawn. You may also have a reaction at the site where the HPV vaccine is injected into your muscle. These reactions include redness, swelling, itching, soreness, or pain. Fainting can occur after vaccination, most commonly among teenagers and young adults. Although fainting episodes are uncommon, we will observe you for at least 15 minutes after you receive your HPV vaccine. You may also have symptoms that make you feel like you have the flu such as fever, fatigue, and body aches, but these symptoms are less common and go away quickly.

There is a remote possibility that you could have an allergic reaction to the vaccine including diffuse itching, hives, rash, wheezing or swelling of the throat. Some allergic reactions could be severe and even life threatening, but these reactions are very rare. You will not be allowed to receive the HPV vaccine if you are known to be allergic to any of the components in the vaccine.

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The side effects associated with vaccination with the quadrivalent HPV vaccine are summarized in the table below:

Likely	Less Likely	Rare
➢ Injection site reactions, including: ○ Pain ○ Swelling ○ Redness ○ Itching ➢ Fever ➢ Nausea ➢ Dizziness ➢ Vomiting ➢ Fainting	➢ Headache ➢ Joint pain ➢ Aching muscles/ body aches ➢ Unusual tiredness or weakness ➢ Swollen glands (in your neck, armpit or groin) ➢ Generally feeling unwell	➢ Allergic reactions that may include: ○ Difficulty breathing ○ Wheezing ○ Hives ○ Rash ➢ Guillan-Barre syndrome- a rare disorder associated with progressive weakness in the muscles of the body.

It is not known whether individuals with HIV infection will have more severe injection site reactions or flu-like symptoms associated with receiving the HPV vaccine. The likelihood of more severe reactions is low as the HPV vaccine is made from recombinant proteins and is not a live virus vaccine. It is also unknown whether receiving the HPV vaccine will increase HIV levels, especially in individuals who are not receiving antiretroviral treatment. Finally, antibody levels induced by the HPV vaccine may not be as high or last as long in HIV-infected individuals because of their underlying immune suppression.

Optional Studies

We would like to keep some of the blood samples that are collected for future research. These specimens will be identified by a number and not your name. The use of your specimens will be for research purposes only and will not benefit you. It is also possible that the stored specimens may never be used. Results of research done on your specimens will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you decide now that your blood samples can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood samples. Then any blood samples that remain will be destroyed.

Please read each sentence below and think about your choice. After reading each sentence, please circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My blood samples may be kept for use in research to learn about, prevent, or treat cancer.

   Yes No Initials_____

2. My blood samples may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   Yes No Initials_____

3. Someone may contact me in the future to ask permission to use my specimen(s) in new research not included in this consent.

   Yes No Initials_____

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Study Support

The biopharmaceutical company Merck is the manufacturer of the quadrivalent HPV vaccine. The vaccine is marketed under the brand name GARDASIL®. As part of an agreement between Merck and the National Cancer Institute, Merck is providing the vaccine that is being used in this study. Some of your blood specimens will be sent to Merck so that they can determine the levels of antibody your make to the different types of HPV that are in the vaccine. This will allow us to compare how well the vaccine induces antibodies in patients in this study with the antibody levels obtained in the thousands of patients Merck has already studied that have received the vaccine.

<u>Potential Benefits of Participation</u>

Vaccination with the quadrivalent HPV vaccine may induce immune responses i.e. neutralizing antibody titers to HPV that are comparable to those that have been demonstrated to be associated with prevention of genital warts, precancerous lesions and cervical cancer caused by HPV types 6, 11, 16, 18. In healthy HIV negative women, the vaccine was demonstrated to be highly efficacious in preventing pre-neoplastic and neoplastic conditions associated with persistent HPV infection. In addition, individuals who were already infected with 1 or more of the HPV types in the vaccine prior to vaccination were protected from clinical disease caused by the remaining HPV types, suggesting there is potential for protective benefit even in those individuals who may have already been exposed to or acquired HPV.

On the other hand, it is possible that the quadrivalent HPV vaccine will not stimulate the production of antibodies as well in individuals with HIV infection, and if it does, the magnitude and duration of the HPV antibody response may not be sustained as has been observed in HIV negative individuals. Whether or not individuals receive direct benefit form participating in this study, there is indirect benefit gained for the HIV-infected population in general from determining the safety and immunogenicity of the HPV vaccine and identifying whether additional primary or boosting doses of vaccine may be necessary to achieve antibody levels that have been shown to protect individuals from HPV acquisition.

Research Subject's Rights

Participation in this protocol is totally voluntary and you many withdraw your consent to participate at any time during the course of the study. If you discontinue participation in the study, you will be referred back to your regular physician for medical care.

Upon completion of this study, you may be given the option to participate in additional research protocols if there are appropriate studies for you being conducted at that time. If there is no suitable research study you may be referred back to your referring physician or institution, or to alternative sources of care closer to home. It is important that you understand and agree that participation in this protocol does not constitute a promise of long-term medical care here at the NIH Clinical Center.

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Alternative Approaches or Treatment

The decision not to participate in this study will not compromise your eligibility for other studies in the future. If you choose not to participate in the study, you will be referred back to your regular physician for medical care. If you are a female between 9 and 26 years of age, you may receive the quadrivalent HPV vaccine through your local physician or public health clinic.

Circumstances Under which You May be Withdrawn From the Study

Your participation will be terminated without your consent if you become pregnant, the HPV vaccine becomes unavailable or if safety issues are identified in this study or reported by the vaccine manufacturer that would adversely impact your health. Use of investigational antiretroviral drugs or drugs that may suppress your immune system and your ability to respond to the vaccine, will result in discontinuation of participation in this protocol. You may be withdrawn from the study if any health or other condition occurs under which continued participation to the study might be deemed dangerous to you. Participation will be discontinued if you are unable to meet the requirements of the study, including failure to keep appointments or to take medications as directed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process http://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide.pdf. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to NIIH.

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OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator Lauren V. Wood, M.D., (301) 402-0199. Other researchers you may call are: Brenda Roberson, RN, OCN, (301) 435-4733; Claudia Derse-Anthony, RN (301-443-4237, Jay A. Berzofsky, M.D., Ph.D., (301 496-6874. If you have any questions about the use of your tissue or blood specimens for future research studies, you may also contact the Office of the NCI Clinical Director: 301-496-4251.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

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COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 26, 2010 THROUGH JULY 25, 2011.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____