Prospective longitudinal study on immunogenicity, induction of cellular immune responses and safety of vaccination against HPV with the 9valent vaccine in HIV-positive women

The Papillon study

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INFORMATION VITAL TO YOUR DECISION TO TAKE PART

Introduction:

You are being invited to take part in a clinical study about the immunological efficacy and the safety of the 9valent vaccine (Gardasil9®Merck) against papillomavirus responsible of the cervical, vulvar and vaginal cancer.

This is known as giving “informed consent”.

Please read carefully these few pages of information carefully and feel free to ask any questions you want to the investigator or his/her representative.
There are 2 parts to this document: the information itself and then your written consent.

If you take part in this clinical study, you should be aware that:

- This clinical study is being conducted after having been reviewed by the ethics committee of the CHU Saint-Pierre Hospital and the AFMPS.
- Your participation is voluntary and must remain free from any coercion. It requires the signature of a document expressing your consent. Even after having signed this document, you can stop taking part by informing the investigator. Your decision not to take part or to stop taking part in the study will have no impact on the quality of your care or on your relationship with the investigator.
- The data collected on this occasion are confidential and your anonymity is guaranteed during publication of the results.
- Insurance has been taken out in case you should suffer any damage in connection with your participation in this clinical study.
- You will not incur any charges for the visits specific to this study.
- You may contact the investigator or a member of his/her team at any time should you need any additional information.

Objectives and description of the study protocol:

We are inviting you to take part in a clinical study about the immunological efficacy and the safety of the 9valent vaccine (Gardasil9®Merck) against papillomavirus responsible of the cervical, vulvar and vaginal cancer and will include more or less 200 patients in our medical centre.

Papillomavirus infection (also called HPV) can be responsible for the development of the cervical, vaginal, vulvar, anal and mouth cancer. This infection as well as the precancerous and cancerous lesions that it generates are more frequent in HIV positive patients. In Belgium several vaccines against papillonavirus are commercially available. These vaccines against Papillomavirus do not contain living virus and therefore cannot transmit the HPV infection.

Before the vaccine availability several studies including more than 80.000 person (principally girls and women aged 12 to 45 years old) demonstrated that the vaccine is effective and well tolerated by the general population. Some other studies have also been conducted with two of the three existing vaccines (Cervarix®GSK et Gardasil®Merck) and showed that they are affective and well tolerated by HIV-positive persons. In particular, the vaccination against HPV does not impact the level of the CD4 lymphocytes nor the VIH viral load. These two vaccines protect against the HPV 16 and 18 strains. However, HIV positive people also suffer from HPV infections rarely found in the general population. At CHU Saint-Pierre, in a preliminary study including more than 500 HIV positive women we demonstrated that less than 30% of women had HPV 16 or 18 infection but up to 82% of the patients had an infection by a HPV strain Gardasil9 ®Merck protects against.

This vaccine is more recent and similar to the Gardasil that protects against HPV6/11 (responsible of the condyloma) and 16 and 18(responsible for 70% of the cervical cancer); however, it protects also against 5 others HPV cancerous types (HPV 31/33/45/52/58) and therefore offers a protection against 90% of the cervical cancers). Currently, there is no study that has measured the antibody response in HIV positive women and girls vaccinated with Gardasil9®Merck. Therefore we offer to vaccinate you with this vaccine Gardasil9®Merck that covers better the HPV types founded in HIV positive women. This vaccine is already available on the Belgian market.

Recent studies including several thousands of HIV-negative adolescents and women have shown that a vaccine schedule given in 2 doses (at 0 and 6 months) is as efficient as in a 3-doses schedules (0, 2 and 6 months).However, the 2-doses schedule has not been studied in HIV-positive persons.

In this study, we will compare giving Gardasil9 in2-doses (at 0 and 6 months) or 3-doses schedules (0, 2 and 6 months).

If you participate in the study, you will receive the vaccine either in 2 doses (0 and 6 months) or in three doses (at 0, 2 and 6 month) after random allocation thanks to a computerized program. The vaccine efficacy will be measured by a blood sample that analyses the antibody level that you will develop one month after the last vaccine. These antibodies are proteins able to neutralize the HPV virus. Most people have little or no antibodies against HPV because this virus causes infections that remain on the surface of the human body and not in his inside depth.

The vaccine main point is to induce or increase the production of antibodies by your immune system to protect you against these HPV strains.

Before the vaccination, a blood sample and a cervical smear will be performed to define if there is already an HVP infection and if you already have antibodies against some HPV strains. A cervical smear will also be done at the end of the study.

We expect that the 2-doses regimen will give the same protection as the 3-doses schedule in at least 80% of the participants ; however, if antibodies are absent at month 7 measurement after the 2 doses schedule, a third booster dose will be given in order to obtain the same protection as the three-doses schedule. Safety data on vaccination against HPV duration pregnancy are very reassuring. However, the Superior Health Council in Belgium and the European Medicine Agency recommend to postpone vaccination to after pregnancy. Therefore, to

participate to this study, you had to be already using an efficacious contraception method and we ask you to continue to use it at least up to 1 month after the last vaccine dose.

Course of the study:

Your participation in the study consists in 4 to 5 visits and 2 to 3 phone calls over a period of 18 months. Two or three more facultative visits can be added if necessary.

Visit N°1

The first visit will include:

- A urine test to exclude an unknown pregnancy
- A 10 ml blood sample (corresponding to two teaspoons) will be collected to measure the antibodies against HPV before the vaccination and a sample to measure the CD4 level (one tube) and the HIV viral load if the last results are from more than 6 months
- A cervical smear taken by one of the CETIM gynecologist Dr Manigart, Gilles or Barlow to detect the presence of the papillomavirus on the cervical and if there are some lesions associated to the papillomavirus if there is no previous sample up to 6 months before baseline. This smear will not be performed if there has never been previous sexual intercourse
- Allocation to one of these vaccination schedules by a computarised program of randomisation :
    - 2 doses (at 0 and 6 months)
    - 3 doses schedules (0, 2 and 6 months)
    - You will be immediately informed of the allocation result.
- Administration of the first dose of vaccine: it is an intramuscularly injection in the upper arm (as for any other vaccine)

Phone call N°1

Will take place 3 to 7 days after the injection by the research team to evaluate with a short questionnaire your tolerance of the vaccine. Most of the vaccine side effects are mild local reactions such as sensitivity, slight swelling or redness. If you wish or if there is an important reaction, you will be asked to come to the research centre for a visit and a reaction evaluation.

Visit N°2 (optional)

This visit will take place if you wish or if you present a reaction to the vaccine.

Visit N°3 Only if you receive the vaccine in 3 doses

This visit will take place 2 month after the first dose of vaccine to:

- Make a urine test to exclude an unknown pregnancy
- To administrate the second dose of the vaccine

Phone call N°2 Only if you receive the vaccine in 3 doses

Will take place 3 to 7 days after the injection by the research team to evaluate with a small questionnaire your tolerance of the vaccine. Most of the vaccine side effects are non-significant local reactions such as sensitivity, slight swelling or redness. If you wish or if there is an important reaction, you will be asked to come to come to the research centre for a visit and a reaction evaluation.

Visit N°4 (optional) Only if you receive the vaccine in 3 doses

This visit will take place if you wish or if you present a reaction to the vaccine.

Visit N°5 Only if you receive the vaccine in 3 doses

Visit N°3 Only if you receive the vaccine in 2 doses

This visit will take place 6 month after the first dose of vaccine to:

- Make a urine test to exclude a unknown pregnancy
- To administrate of the second dose of vaccine

Phone call N°3 Only if you receive the vaccine in 3 doses
Phone call N°2 Only if you receive the vaccine in 2 doses

Will take place 3 to 7 days after the injection by the research team to evaluate with a small questionnaire your tolerance of the vaccine. Most of the vaccine side effects are non-significant local reactions such as sensitivity, slight swelling or redness. If you wish or if there is an important reaction, you will be asked to come to come to the research centre for a visit and a reaction evaluation.

Visit N°6 (optional)
This visit will take place if you wish or if you present a reaction to the vaccine.

Visit N°7 Only if you receive the vaccine in 3 doses
Visit N°5 Only if you receive the vaccine in 2 doses
This visit will take place 7 month after the first dose of vaccine to make a blood sample, 3 tubes 10ml blood (corresponding to 6 teaspoons) to measure the antibodies against HPV, the CD4 level and the HIV viral load after the vaccination

Visit N°8 Only if you receive the vaccine in 3 doses
Visit N°6 Only if you receive the vaccine in 2 doses

- This visit will take place 18 month after the first dose of vaccine to make a blood sample, 3 tubes 10 ml blood (corresponding to 6 teaspoons) to measure the antibodies against HPV .A cervical smear taken by one of the CETIM gynecologist Dr Manigart, Gilles or Barlow to detect the presence of the papillomavirus on the cervical and if there are some lesions associated to the papillomavirus if there is no previous sample up to 6 months before baseline. This smear will not be performed if there has never been previous sexual intercourse.

Visit N°7 Only if you receive the vaccine in 2 doses (optional)

This visit will take place only if your results from blood test done on month 7 (visit N°5) show that antibodies against HPV have not been developed. A third dose will then be given as a booster.

Possible risks:

Subsequently to a blood sampling, you may feel dizzy, mild pain, bruising, skin irritation or redness may occur at the place where the blood is taken from. Usually these reactions aren't important and last just for a few hours or days.
During the vaccine injection, you may feel a minor discomfort or some pain localized around the injection site. We will ask you to lie down for 15 minutes after the administration of the vaccine.
A minor discomfort or some pain, a bruise or redness can appear on the vaccine site. Usually these reactions aren't important and just for a few hours or days.

Possible benefits:

You will receive a vaccination that gives a very good protection against the infection by 9 strains of papillomavirus. A smear with an extensive research on the HPV infection will be performed at the

beginning and at the end of the study; usually this HPV research isn't performed during routine gynecology exams. You will participate in a study that will provide valuable information on the tolerance and the efficacy of this vaccine in HIV positive women.

Participation / Withdrawal from the study:

Your participation in this project is voluntary and involves no financial cost. The physician of the research team will answer any further questions relating to this study. If you agree to be in this study, you will have to sign this consent form and you will receive a signed copy of it.
It is your choice whether you want to take part in it or not. No matter what you decide, all the services you may receive at this clinic will remain the same. You also have the right to stop your participation in the study at any time, even after you have signed this Informed Consent Form. You do not have to give a reason explaining this decision.

Samples collected for the analyses described for the study in this document:

All the blood samples for the anti-HPV antibodies will be centralized in the Infectious Diseases department - Saint-Pierre University Hospital. After, the samples will be sent to the USA in the Merck laboratory where the anti-HPV antibodies analyze will be performed. The surplus of your samples will be destroyed once the analyses described in this document have been carried out, i.e. in principle in minimum 10 years.

Information provided from tests done on your samples will not be given to you. This information will not be placed in your medical records and will have no effect on your medical care.

Information provided from tests done on your samples to measure the antibodies will not be given to you. This information will not be placed in your medical records and will have no effect on your medical care.

On the other side, the information provided by tests done on your samples to measure your viral load and your lymphocytes CD4 counts will be communicated to you and will be included in your medical records.

The gynecological samples (smears) will be sent to the reference laboratory for HPV (AML in Antwerp) for the research on HPV and on cervical precancerous lesions. Information provides from these tests will be communicated to you and will be included in your medical records.

If you take part in this clinical study, we ask you:

- To cooperate fully to the smooth running of this study.
- Not to conceal any information relating to your state of health, the medication you are taking or the symptoms you are experiencing

Confidentiality:

The data collected on this study are confidential and your anonymity is guaranteed (all personal data will be anonymized by a unique code).
Your personal information (age, gender, current treatment, ect.) will also be recorded. Your personal information will be kept strictly anonymously and will be disclosed only to investigators involved in this study. This information may also be examined by the study team and by the Belgian regulatory to check that the information is correct. Your name will not appear in any reports or publications.

Insurance:

The Infectious Diseases department - Saint-Pierre University Hospital has obtained an insurance as sponsor of the study, as required by article 29 of the Belgian law of 7 may 2004 on the rights of study participants in research projects that is intended to cover potential harms in relation to your participation in the study.

If you experience any harm or have questions on injuries or complications as a result of being in the study, please contact the responsible researcher or physician in the clinic where the study takes place.

Contact:

For more information, please contact the Principal Investigator of this study: Dr Konopnicki Deborah through the Infectious Disease Department 02 535 41 31 from 8.30am to 5pm from Monday to Friday or by email deborah_konopnicki@stpierre-bru.be

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Inform consent for the patient

1. Participant

My signature below constitutes my acknowledgment that:

- I have been informed of the nature of the study, its purpose, its duration, any risks and benefits and what is expected of me
- I have had the opportunity to ask any questions that came to mind and have obtained a satisfactory response to my questions
- I know that I can ask questions at any moments of this study
- I understand that my participation in this study is voluntary and that I am free to end my participation in this study without this affecting my relationship with the therapeutic team in charge of my health.

I understand and consent that data about me will be collected throughout my participation in this study and that the investigator and the sponsor of the study will guarantee the confidentiality of these data. I have received a copy of the information to the participant and the informed consent form.

Date: ……

Name: ……

Signature of the volunteer: ……..

2. Witness/Interpreter

I was present during the entire process of informing the patient and I confirm that the information on the objectives and procedures of the study was adequately provided, that the participant (or his/her legal representative) apparently understood the study and that consent to participate in the study was freely given.

Date: ……

Name and qualification: ……

Signature of the Witness/Interpreter: ……..

3. Investigator

I confirm that I have verbally provided the necessary information about the study and have given the participant a copy of the information document.
I confirm that no pressure was applied to persuade the patient to agree to take part in the study and that I am willing to answer any additional questions if required.
I confirm that I operate in accordance with the ethical principles set out in the latest version of the "Helsinki Declaration", the "Good Clinical Practices" and the Belgian Law of 7 May 2004 related to experiments on humans.

Date: ……

Name: ……

Signature of the investigator: ……..