TITLE:

PROPHYLACTIC VACCINES AS THERAPY: PREVENTION OF RECURRENCE OF EXTENSIVE GENITAL WARTS

SUBTITLE:

THE EFFECTS OF PROPHYLACTIC HPV VACCINE ON HPV RELATED DISEASE AND TYPES IN WOMEN WITH GENITAL WARTS

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Author:
Prof Greta Dreyer

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1. INTRODUCTION

The global burden of HPV disease as represented in genital warts is very high, which in turn leads to high costs of healthcare and loss in quality of life [1-4]. The prevalence of HPV in Sub Saharan Africa is among the highest in the world [5-7]. In South Africa, extensive genital warts are not an infrequent finding in general gynaecology and oncology clinics, but accurate prevalence data are unavailable. Recently the occurrence of these lesions increased as HIV-related immune-compromise became more frequent [8,9]. Large, extensive or recurrent genital warts are more frequent in women with HIV related immunodeficiency and therefore this population provides unique opportunity to study changed viral epidemiology, immunity related research questions and novel treatment approaches.

The HIV epidemic causes large numbers of women to have a poor immunity, which makes them susceptible to opportunistic disease or more extensive viral disease. The HIV epidemic may also change the epidemiology of HPV viral disease as shown in cervical HPV related disease, causing changes n HPV type distribution and in the prevalence of HPV in the general population.

The financial and psycho-social burden of genital warts is well described and widely accepted in the developed world. Medical and destructive therapy for warts is generally very effective [10-13]. The unique problems posed by large or extensive genital warts are, however, not so easily solved and treatment of affected individuals remain very challenging.

Management options for these lesions currently include mostly surgery and cauterization because the lesions and affected area is too large for conservative medical treatment. Surgery often has disfiguring results and recurrence remains very frequent with all treatment modalities.

Recent data suggests that one of the reasons for recurrent or huge papilloma virus induced warts is the absence of antibody response in selected individuals [8,14,15]. In addition, data from recurrent respiratory papilloma cases suggest that vaccination with preventative quadrivalent vaccine can be therapeutic in many of these patients [16-18].

It is anticipated that the additional stimulation from a vaccine against the common wart-inducing HPV types (6 and 11) can help increase the production of protective antibodies in these susceptible women and can contribute to control the disease. In this prospective randomized trial, women with extensive genital warts will be studied, comparing those who have received quadrivalent HPV vaccine to a control group of women who have received hepatitis B vaccine.

2. HYPOTHESIS AND AIMS

The **main hypothesis** is that HPV preventative vaccine can play a role in the control of non-neoplastic HPV disease in women with and without HIV infection through the high antibody response elicited. In addition, it is the hypotheses of this study that:

- HPV types in genital warts are affected by vaccination with HPV4

- In a population with a high prevalence of HIV, the HPV type distribution differs from the published data
- HPV vaccines will have an effect on cervical HPV types and disease status
- The size or recurrence rate of extensive genital warts can be reduced by vaccination with HPV4 after surgical treatment

3. METHODS

This will be a multi-centric study done at two different sites in South Africa, e.g. Pretoria Academic Hospitals, Stellenbosch University Hospital.

Patient selection:

Female patients referred or presenting with genital warts at each site will be eligible and evaluated against the inclusion and exclusion criteria.

Women who are clinically or severely immune-compromised will not be included into the study, but both HIV negative and HIV infected women will be included. Fifty women with large or recurrent genital warts will be recruited for this study from 2 sites in South Africa.

Inclusion criteria:

- Female patient > 16 years
- Presence of problematic vulvo vaginal genital warts:
  Largest tumour diameter > 3 cm
  OR Tumour on labia minora and labia majora OR bilateral > 1 cm each side
  OR Tumour in vagina/cervix as well as on vulva > 1 cm lesion each
- HIV negative
- HIV infected:
  CD4 ≥ 300 x 10^6 cells/l
  OR viral load controlled
  OR ARV compliant > 6 months

Exclusion criteria:

- Pregnant of planned pregnancy within 6 months
- Not able to comprehend study method or not able to attend all study visits
- Previous HPV vaccination
- Active known opportunistic infection or malignancy including PCP, PTB, oesophageal Candida or Kaposi sarcoma or lymphoma
- Known allergy to vaccines or content of vaccine
- Previous radiation for genital warts

Recruitment:

Women with genital warts will be evaluated for inclusion into the study. Those who fit the inclusion criteria and are without any of the exclusion criteria will be fully informed and invited to participate.

The first target will be to recruit the first fifty consecutive eligible patients who have signed written consent; recruitment for the study will be done for at least 24 months.

First clinical visit:

- Evaluation genital lesions:
  On study entry tumour size and position will be documented graphically (see Appendix B diagram) and photographically and viral typing from the vulva wart and cervix will be done using Roche LA test.
- Evaluation immune status:
  HIV status and CD4/CD8 count will be recorded and tested and the serum will be collected for antibody testing. Cervical disease of clinical significance will be excluded or treatment offered if relevant.
- Randomization:
  Patients will be randomized to receive either HPV4 or Hepatitis B vaccine.
- Vaccination:
  The participants assigned to the test group will be administered HPV4 vaccine in three doses as recommended by the manufacturer. Participants assigned to the control group will receive Hepatitis B vaccine in three doses as recommended by the manufacturer.

Follow-up clinical visits: week 8, week 16 and week 24:

- Evaluation genital lesions:
  Three follow up visits will be scheduled two months apart at which time the lesion size will be recorded.
- Evaluation immune status:
  After month 6 or the third visit, the serum will again be collected for antibody level testing.
- Treatment decision:
  According to the clinical response as measured at month six and onwards, locally destructive or surgical treatment will be allowed according to the preference of the clinician and as determined by clinical factors.

Follow up after treatment:

- Follow up will be done at six monthly intervals.
- Evaluation genital lesions:
  At these visits lesion size will be determined and documented. HPV typing on the cervical and vulval lesions will be repeated at least once.
- Further treatment of warts:
  If needed, repeat surgery and/or local destruction will be allowed and documented. These will be around week 48 and week 72, or study exit.

Study exit:

- Participants will exit the study in week 72.

- In the absence of harm as determined at interim analysis or suggested by participant disease history, researchers will be unblinded for participant status at study exit and alternative vaccines will be offered to each of these women.

Outcome measures:

Outcome measures will be: change in size of lesions before and after vaccination; incidence, time and size of recurrent disease; change in HPV type specific antibody titres before and after vaccination; change in prevalence of vaccine types HPV DNA on the cervix before and after vaccination; and change in prevalence of vaccine types HPV DNA in the warts after vaccination.

4. DATA COLLECTION AND HANDLING

Data will be collected prospectively as described above. Hand drawings of the affected areas will be made at each visit (see Appendix B diagram). In addition, a standardised photograph will be taken of the vulvo-vaginal area for future comparison. The lesion diameters will be measured and noted. Data sheets will be used to collect all clinical and laboratory results. Data entry into a designed data base will be done from 12 months onwards until all patients have completed a follow up period.

Analysis will be done of the pre-and post-vaccination antibody levels, immune status and HIV status and comparison of the above measures with the HPV and HPV-associated disease outcomes will be made.

5. ETHICAL CONSIDERATIONS

The study protocol will be submitted for approval to the relevant ethics committee. Participation in this study is completely voluntary.

All participants will receive written information about the study which they may retain, and will give written consent to participate prior to study entry. Patients undergoing treatment will be informed and will give previous written informed consent as per standard protocol of the treatment facility.

6. COLLABORATION

This study will be performed in collaboration with the VACCS consortium – colleagues from the Universities of Pretoria and Stellenbosch.

7. BUDGET AND FUNDING

The preliminary budget for this investigator initiated study is attached. Vaccine donations will be sought. The investigators have applied for funding at various funding bodies and are awaiting the evaluation results.

8. RESEARCH REPORTING

The research analysis and reporting will be done independently from all sponsoring groups, but all collaborating parties will be invited to comment and approve manuscripts before final submission. Authorship of any resulting manuscript will follow Vancouver guidelines for contribution and intellectual input. Any conflict of interest and contribution to funding will be reported in all research output from this trial. The results will be reported and submitted to appropriate national and international forums and publications.

9. REFERENCES

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PATIENT INFORMATION LEAFLET

TITLE OF THE RESEACH PROJECT:
THE EFFECTS OF PROPHYLACTIC HPV VACCINE ON WOMEN WITH GENITAL WARTS: HPV RELATED DISEASE AND TYPES (Ref number 21/2016)

Dear Patient,

1) INTRODUCTION
You are invited to volunteer for a research study. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this leaflet, do not hesitate to ask the investigator. You should not agree to take part unless you are completely happy about all the procedures involved. In the best interests of your health, it is strongly recommended that you discuss with or inform your personal doctor of your possible participation in this study, wherever possible.

2) THE NATURE AND PURPOSE OF THIS STUDY
The aim of this study is to test the effect of a HPV vaccine before and after treatment of large genital warts. We will test this by administering the vaccine to some patients and a hepatitis vaccine to all others.

3) EXPLANATION OF PROCEDURES TO BE FOLLOWED
You have been diagnosed with large genital warts. The routine treatment for this condition is to remove the wart(s) surgically. These warts are caused by infection with the human papillomavirus (HPV). In this study we test if vaccination with the HPV vaccine will have an effect on the wart(s).

During the study you will receive 3 doses of vaccine at scheduled visits, and details of the wart(s) will be documented on your file. After the last dose of vaccine, all warts that still need treatment will be treated. At follow up visits we will document and treat (if necessary) any wart that remains or re-appears.

We will also render specialised care for possible linked cervical disease (in the mouth of the womb).

4) RISK AND DISCOMFORT INVOLVED.
You may experience discomfort in the arm where the vaccine is given. You may still need treatment for your warts even if the vaccine is effective.

5) POSSIBLE BENEFITS OF THIS STUDY.
The vaccines administered may be beneficial in that it can prevent future infections. You will receive the same quality of care as patients usually do who are not taking part in the study. You will not be receiving any money or other benefits because of participating in the study. However, we will be grateful for your participation as the information from this study will assist us to learn more about development of this disease.

6) HIV INFECTION
It is possible that you are HIV infected and you know about this. We also would like to know this fact so that we can use this to interpret our research results.

7) I understand that if I do not want to participate in this study, I will still receive standard treatment for my illness.

8) I may at any time withdraw from this study.

9) ETHICAL APPROVAL

This Protocol was submitted to the Faculty of Health Sciences Research Ethics Committee, University of Pretoria and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki (last update: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human/subjects.

10) INFORMATION

If I have any questions concerning this study, I should contact:
XXXXXX Tel no YYYYYYYYY

12) CONFIDENTIALITY

All records obtained whilst in this study will be regarded as confidential. Results will be published or presented in such a fashion that patients remain unidentifiable.

CONSENT TO PARTICIPATE IN THIS STUDY

I have read or had read to me in a language that I understand the patient information leaflet before signing this consent form. The content and meaning of this information have been explained to me. I have been given opportunity to ask questions and am satisfied that they have been answered satisfactorily. I understand that if I do not participate it will not alter my treatment in any way. I hereby volunteer to take part in this study.

Patient name ……..
(Please print)

…… ……
Patient signature Date

I, Dr …….. herewith confirm that the above patient has been informed fully about the nature, conduct and risks of the above trial.

Investigator name ……
(Please print)

…… ……
Investigator signature Date

Witness name ……
(Please print)

…… ……
Witness signature Date

VERBAL PATIENT INFORMED CONSENT (applicable when patients cannot read or write)

I, the undersigned, Dr ……, have read and have explained fully to the patient, named …….. and/or his/her relative, the patient information leaflet, which has indicated the nature and purpose of the study in which I have asked the patient to participate. The explanation I have given has mentioned both the possible risks and benefits of the study and the alternative treatments available for his/her illness. The patient indicated that he/she understands that he/she will be free to withdraw from the study at any time for any reason and without jeopardizing his/her treatment.

I hereby certify that the patient has agreed to participate in this study.

Patient name ……
(Please print)

Investigator name ……..
(Please print)

…….. ……
Investigator signature Date

Witness name ……..
(Please print)

…… ……
Witness signature Date
(Witness sign that he/she has witnessed the process of informed consent)