Study title: Screening for HPV and cervical cancer in young women with perinatally acquired HIV (SHiP study)

Study type: An observational study to determine cervical cytological abnormalities and HPV prevalence amongst young women aged 18 or over with perinatally acquired HIV.

Internal Reference / Short title: SHiP
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Main sponsor: Imperial College London
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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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LIST OF ABBREVIATIONS

HPV	Human Papilloma Virus
Hr-HPV	High-risk Human Papilloma Virus
ART	Antiretroviral therapy
HIV	Human Immunodeficiency Virus
PaHIV	Perinatally acquired HIV
WLWH	Women living with HIV
CIN	Cervical Intraepithelial Neoplasia
VIA	Visual Inspection with Acetic acid
BHIVA	British HIV Association
HYPNet	HIV in Young People Network
NSC	National Screening Committee
NHS	National Health Service
PHE	Public Health England
WHO	World Health Organisation
NHSCSP	NHS Cervical Screening Programme
PCR	Polymerase Chain Reaction
GCP	Good Clinical Practice
IEC	Independent ethics committee
IRB	Institutional Review Board
PI	Primary investigator
REC	Research Ethics Committee

1. TRIAL SUMMARY

Title: Screening for HPV and cervical cancer in young women with perinatally acquired HIV (SHiP study)

Summary: This protocol describes an observational study of cervical cytology assessment, high risk human papilloma virus (hr-HPV) status, and HPV antibody titres amongst adult women living with perinatally acquired HIV infection (PaHIV). Eligible consenting participants will have two samples taken; firstly, a cervical sample tested for cytology and Hr-HPV with the Cepheid GeneXpert HPV; secondly, Blood sampling, serum will be assessed for hr-HPV serology. All women with PaHIV, vaccinated and unvaccinated for HPV, over the age of 18 years will be eligible and will be recruited into one of two cohorts: (1) sexually active women: full study, cervical and blood sampling (n=50) or (2) non-sexually active women, blood sampling only (n=30). Follow up for abnormal smear results or hr-HPV positivity will be arranged through standard NHS referral pathways for colposcopy.

Rationale: HIV increases the risk of HPV related cervical intraepithelial neoplasia (CIN) and cervical cancer, and it is hypothesized that women with perinatally acquired HIV may be more at risk from an earlier age than the general population, and than women living with HIV acquired in adulthood, although there is little data to support this. For this reason, the HIV in Young People Network (HYPNet) guidelines state that cervical screening should start when a young woman with PaHIV becomes sexually active, irrespective of age(1), but despite these recommendations this is not included in UK guidelines. Currently cervical cytology is routinely available for all women with HIV yearly from the age of 25 to 65 in England, but younger women (<25 years) with PaHIV are not currently eligible for NHS cervical screening.

We hypothesise that young women with PaHIV may benefit from cervical screening < 25 years of age, due to an increased risk of cervical abnormalities as a consequence of lifelong impaired immune function and the potential for suboptimal responses to the HPV vaccination. A delay in screening until aged 25 may miss early detection of manageable pre-cancers and cancer.

Primary aim: To identify the prevalence of abnormal cervical cytology in a cohort of sexually active young women with PaHIV aged $\geq$ 18 years

Secondary aims:

- To identify the prevalence of high-risk HPV by subtype in a cohort of sexually active women with PaHIV aged $\geq$ 18 years
- To identify the prevalence of CIN2+ in a cohort of sexually active women with PaHIV aged $\geq$ 18 years
- Explore the use of HPV testing as a primary screening tool compared with cervical cytology in this cohort
- Characterisation of immunological and other correlates with high-risk HPV carriage, cervical abnormalities and CIN2+
- Investigate antibody titres to the HPV in vaccinated and unvaccinated women and compare this to the antibody responses to other vaccinations (e.g. hepatitis B)

- Explore the relationship between HPV-antibody titres and current immune function (CD4 count) and CD4 count at the time of vaccination
- Explore the uptake and acceptability of cervical screening before the age of 25 in this cohort
- Explore the cost-benefit of providing cervical screening before the age of 25 in this cohort

Planned sample size: 80

Sites:

900 Clinic Imperial College Healthcare NHS Trust
Team clinic, Mortimer Market Centre, Central and North West London NHS Foundation Trust

Planned Study Period: Sept 2019 – Sept 2021

2. STUDY BACKGROUND

Cervical cancer is caused by high-risk HPV subtypes, and the relationship between HIV and HPV is well recognised. In HIV uninfected women HPV 16 and HPV 18 are responsible for 71% of cervical cancers(2). Women living with HIV are more likely to have persistent HPV infections, and are at greater risk of developing complications secondary to this, including cervical dyskaryosis, intraepithelial neoplasia (CIN) and cervical cancer(3–6). It is due to these higher rates as well as the more rapid progression of disease that BHIVA recommends annual smear tests for HIV positive women aged 25-65 years(7), compared to 3-yearly for HIV non-infected women. BHIVA has no specific guidance for women with perinatally acquired HIV (PaHIV) under 25 years due to a paucity of data, but the HIV in Young People Network (HYPNet) state that cervical screening should start within a year of when a young woman with PaHIV becomes sexually active, ideally with baseline colposcopy(1). Due to limitations of national testing policies within the UK this is no longer achieved for those under 25.

Although there are very little data on cervical screening in people with PaHIV, this population is known to be at an increased risk of all cause malignancy, with more than half being associated with chronic oncogenic viral infections(8). It is proposed that the pathogenesis of HPV related disease may be altered in those with PaHIV due to living with the HIV virus throughout childhood and sometimes having significant immunosuppression during this time. Moscicki et al. found that adolescents with primarily horizontally acquired HIV had a much higher rate of high grade squamous intraepithelial lesions (HSIL) at 22% compared with 5% in age- and risk-matched controls(9). In the same cohort, 77% of those with HIV were positive for HPV, and only 30% of these had normal cytology, compared to 55% testing positive for HPV in the HIV-negative controls, of which 70% had normal cytology(10). Brogly et al. also found a higher prevalence (48%) of cervical abnormalities in those with PaHIV who had a smear test compared to that documented in aged matched HIV-negative adolescents(11). In a study looking at HPV infections in non-sexually active PaHIV, 30% of girls had anogenital HPV compared to 7% of HIV-exposed but uninfected girls, although the HIV uninfected girls were significantly younger in age. They suggest that HPV may be commonly acquired non-sexually in PaHIV, and that vaccine efficacy may be different in this group(12). Within our cohort of young adults with PaHIV (the 900 clinic) at Imperial College Healthcare NHS Trust, previous data showed 17% of young women had an abnormal first smear, with a median age of 19 years, and a median coitarche-first smear interval of 2 years. Overall the median age at coitarche was 16 years(13).

In the NHS cervical screening programme, samples are not routinely tested for HPV unless there are borderline or low-grade changes. In 2016, the UK National Screening Committee (NSC) recommended that hr-HPV testing should replace cervical cytology as the primary cervical screening method. NHS England plans to achieve full rollout of this by the end of 2019, and this is already being implemented in some pilot sites across England. Women living with HIV (WLWH) will continue to have annual screening using primary hr-HPV testing rather than cytology(15). Women who are positive for hr-HPV will also have cervical cytology sent to triage whether they should be referred for colposcopy or have repeat screening in one year(15).

Other international guidelines recommend primary cervical screening with hr-HPV(16), and management protocols differ slightly on the referral pathway to colposcopy, with some recommending partial genotyping and direct referral to colposcopy for women testing positive for the highest risk HPV (16 or 18)(17). In our cohort, there is little evidence to determine the best cervical screening algorithm, so for this reason we have elected to offer colposcopy to all women testing positive for hr-HPV as well as those with abnormal cervical cytology.

The GeneXpert HPV Assay (Cepheid, Sunnydale, California, USA) is a clinically validated real-time polymerase chain reaction (PCR) assay, which uses a single-use cartridge for the detection of 14 types of hr-HPV in 3 channels (HPV 16, HPV 18/45, and other hr-HPV 31/33/35/52/58/51/59/39/56/66/68)(18). The NHS Cervical Screening Programme (NHSCSP) lists the Cepheid GeneXpert as acceptable for use within screening for HPV triage and test of cure(19).

Part of the reason for this move to primary screening with HPV in the UK is due to the introduction of the national HPV immunisation programme in 2008. It is thought that the hr-HPV testing is a more appropriate screening method in HPV vaccinated women, as the incidence of CIN should be lower(15). Since 2008, HPV vaccination has been offered to all girls aged 12-13 years (with a catch up programme for the first two years in girls aged up to 18 years). Until 2012, girls were offered the bivalent vaccine (against HPV 16 and 18), and since then the quadrivalent vaccine has been offered (HPV 16, 18, 6 and 11)(20). Studies looking at immunogenicity of the HPV vaccine have showed overall good responses in people living with HIV, with better and more sustained responses in those with a higher CD4 count and undetectable viral load(21–24), although data in people with PaHIV is sparse. A study by Giacomet et al. looked at HPV vaccine safety and response in HIV-infected and -uninfected adolescents in Italy(21). They recruited 46 females and males with HIV aged 13-27 years, and an equal number of age matched controls; the mean CD4 count in this group was 715 cells/ul and 95% had an undetectable viral load at baseline. At one month post vaccine, seroconversion rate was 85% in the HIV positive group compared to 91% in the control group. The mean titres measured using a HPV IgG ELISA kit were 5.8ug/ml less in the HIV positive group at 18 months post vaccine(21). In another study looking at vaccine response by Kahn et al. 99 women with HIV (none perinatally acquired) were recruited, 69 into a non-antiretroviral therapy (ART) group, and 30 into an ART group(22). Overall mean CD4 count was 613 cells/ul, with 86% having a CD4 $\geq$ 350 cells/ul. They found that geometric mean titres (GMT) were around twice as high in the ART group compared to non-ART group, and this was statistically significant for HPV types 16 and 18. They found that GMT was also significantly lower in the non-ART group versus a historical comparison group. Seroconversion rates were 100% for all four HPV types in the ART group but were as low as 92.3% for HPV 18 in the non-ART group and this dropped significantly by week 48 to 67.6%. Titres were also higher at week 28 and 48 in those with VL <400 copies/ml, but this was only significant for HPV 11(22). Lastly, in a study looking at HPV vaccine responses in children with HIV aged 7-12, seroconversion rates were 96% but immune titres to HPV 6 and 18 were 30-60% lower than those achieved in historical controls(25). The clinical significance of this is unclear, and further studies are needed to assess the long-term efficacy of the HPV vaccination in young people living with HIV.

3. STUDY OBJECTIVES

Primary objective: To identify the prevalence of abnormal cervical cytology in a cohort of sexually active young women with PaHIV aged ≥ 18 years

Secondary objectives:

- To identify the prevalence of high-risk HPV by subtype in a cohort of sexually active women with PaHIV aged ≥ 18 years
- To identify the prevalence of CIN2+ in a cohort of sexually active women with PaHIV aged ≥ 18 years
- Explore the use of HPV testing as a primary screening tool compared with cervical cytology in this cohort
- Characterisation of immunological and other correlates with high-risk HPV carriage, cervical abnormalities and CIN2+
- Investigate antibody titres to the HPV in vaccinated and unvaccinated women and compare this to responses to other vaccinations (e.g. hepatitis B)
- Explore the relationship between HPV-antibody titres and current immune function (CD4 count) and CD4 count at the time of vaccination
- Explore the uptake and acceptability of cervical screening before the age of 25 in this cohort
- Explore the cost-benefit of providing cervical screening before the age of 25 in this cohort

4. STUDY DESIGN

This is an observational study of cervical cytology and hr-HPV carriage in young females attending a large tertiary referral centre providing HIV care for perinatally acquired HIV infection (n=80). Recruitment will be over 18 months from the study start date or until the planned sample size is recruited. Consenting study participants will give consent to access HPV vaccination history from GP records with the dates and vaccines received.

Eligible young women (≥ 18 years with PaHIV infection) will be invited to join the study. They will be given time to read the patient information sheet and written informed consent will be taken by a study team member. Women will be recruited into one of two cohorts: (Cohort 1) Aged ≥ 18 and sexually active, (Cohort 2) Aged ≥ 18 and not sexually active.

At enrolment, a single study visit will be required for both cohorts, during which, a venous blood draw of 6mls will be taken plus an optional additional 30mls (36mls total) and an optional urine sample for the Biobank. Participants will be asked to complete a short 1-page questionnaire and a data collection sheet will be completed by study staff. Women enrolled into cohort 1 will also have a speculum examination and a cervical sample will be tested for hr-HPV using the Cepheid GeneXpert HPV and sent for cytology in routine NHS laboratories.

Results of cervical cytology and cervical hr-HPV testing will be given to the study participants in cohort 1. This will either be at an arranged second visit, or via a phone consultation, email or letter depending on the preferences of the individual. Referral to colposcopy services will be made in accordance with current national clinical pathways for any young woman with

abnormal cytology results. In the case of normal cytology in the presence of hr-HPV, these women will also be referred for colposcopic examination. The blood HPV serology are for research purposes only and hence individual results will not be given back to the study participants. At the end of the study, aggregate results will be shared with the study participants.

The HPV vaccination is now available to all women in the UK aged less than 25 years. If women have not been vaccinated at the time of enrolment but are subsequently vaccinated, we will consent them for repeat serological testing at the next clinic appointment following the completion of the HPV vaccine course.

5. PARTICIPANT ENTRY

5.1 Screening

Young adults living with perinatally acquired HIV-1 attending the 900 clinic at Imperial College Healthcare NHS Trust London, or the Team clinic at the Mortimer Market Centre, aged 18 years and older.

5.2 Inclusion criteria

- Cohort 1:
    - PaHIV females age 18 years and older
    - Sexually active
    - Able to give informed consent
- Cohort 2:
    - PaHIV females age 18 years and older
    - Able to give informed consent

5.3 Exclusion criteria

- Cohort 1:
    - Pregnancy
    - Not sexually active
    - Previous total abdominal hysterectomy
    - Unable to give informed consent
- Cohort 2:
    - Unable to give informed consent

5.4 Withdrawal criteria

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason.

Participants who withdraw from the study will have their censored data included in the study analysis unless specifically requested by the individual not to include it. Any stored

samples remaining on withdrawn participants will be either destroyed or remain within the laboratory for future testing depending on the participant's wishes.

The reason for withdrawal will be recorded in the CRF.

6. STUDY PLAN

6.1 Visit summary

The study will consist of one visit, plus an optional second visit, and where possible these will coincide with routine clinical visits:

- Screening, patient information and consent
- Study visit 1 (may be at the same time as screening, provided sufficient time has been given to read the patient information sheet and understand the study) – all participants
- Study visit 2, results – optional for cohort 1

6.2 Screening visit: Patients will be assessed against the above inclusion and exclusion criteria and will be asked if they wish to participate if they are eligible for the study.

To all eligible individuals, an explanation of the study will be provided along with a copy of the participant information sheet. They will be given as much time as they need to consider their participation and will be informed that participation is voluntary and a decision not to participate will not affect their clinical care. The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed, in the presence of a study team member.

Written and verbal versions of the Participant Information and Informed Consent will be given to participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol, and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Optional sub-study: Consent for an additional donation of blood and urine sampling to the Biobank for future research is optional and consent for the use of any remaining blood samples taken as part of this protocol for use in future research into the immune system and viral infections as part of the Communicable Diseases Research Biobank will also be obtained.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate. Written Informed Consent will then be obtained and a copy of the signed Informed Consent will be offered to the participant. The original signed form will be retained.

Visit 1 will either be at the time of the screening visit, their next routine clinic visit or as an additional study visit depending on participant preferences.

6.3 Visit 1: At visit 1 (either the same day as study enrolment or scheduled to another date as per participant preference) each participant will have their eligibility and consent in the trial confirmed. Clinical and demographic information will be recorded on the study CRF and will include:

- Age
- Ethnicity
- Current CD4 count
- Current CD4:CD8 ratio
- Current HIV-1 RNA viral load
- Nadir CD4 count
- Length of viral suppression <50 copies/ml
- Current antiretroviral therapy
- Concomitant medications
- Smoking
- Menarche
- Coitarche
- Obstetric history
- Gynaecology history including previous smear results
- Contraception
- HPV vaccination history (including age at vaccination, type, number of doses)
- Other vaccination history
- CD4 count at time of first HPV vaccination (if known)
- Lifetime number of sexual partners
- Diagnosed STIs
- History of genital warts
- Consent to access GP records for HPV vaccination details where GP aware of status

Investigations:

- Cervical smear test
- Cervical sampling for hr-HPV testing
- Blood for serology
- Optional Blood and urine for Biobank

6.4 Visit 2 (optional for cohort 1, 2-4 weeks later): Attendance for results of the cervical cytology and hr-HPV will be made with the research team. If a participant does not wish to attend for a second visit they will be given the option to get their results by phone, letter or email. All other tests are considered research tests and the individual results will not be given back to the study participant. Any abnormal cervical cytology result will be referred to local colposcopy services in accordance with local and British guidelines. Women who test positive for any hr-HPV will also be referred to colposcopy for the purposes of this study. Consent will be sought to collect outcome data following gynaecology referral.

6.5 Visit 3: For those women who receive HPV vaccination after enrolment into the study, repeat blood tests will be taken at the next clinic visit after completion of the vaccine course.

The study procedures algorithm can be seen in Figure 1.

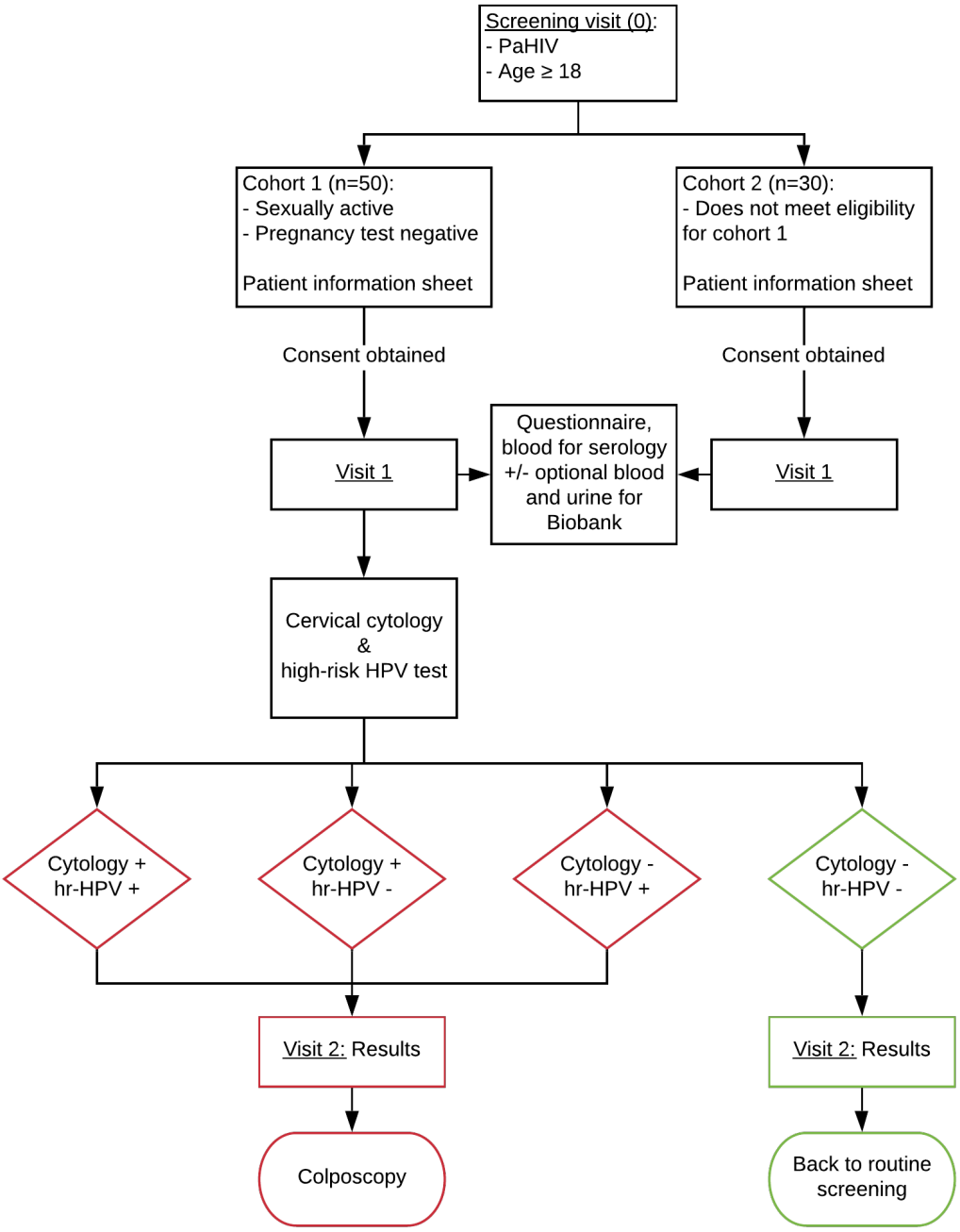

Figure 1: Management protocol for participants

7. STUDY PROCEDURES

7.1 Cervical sampling for smear test and hr-HPV testing

Cervical cytology will be performed by a trained healthcare professional in accordance with current guidance in England for liquid based cytology using a disposable plastic speculum for speculum examination. A 1ml aliquot will be analysed for hr-HPV using the Cepheid GeneXpert HPV.

The risks to the participant of the procedure are discomfort and vaginal bleeding after the procedure. The participant may also feel discomfort vaginally following the speculum examination.

7.2 Venepuncture and urine

Participants will be consented to donate 6mls for serological testing, and an optional additional 30 mls of blood and a urine sample to be stored in the Biobank at Imperial College. This will be used for additional research testing for future viral and immune studies. Where possible blood taking will coincide with routine clinical monitoring blood taking.

The risks to the participant of venepuncture are pain and bruising following the procedure. The participant may also feel faint due to a vaso-vagal response or hypotension, and in this case the venepuncture will cease and the patient will be laid flat until recovery.

HPV antibody serology: 1 x Red top 6 mls

BioBank EDTA: 5 x purple top 6ml to 30 mls

Total samples at Visit 1:

* Blood: One 6ml Red top tube: 6ml

* Blood: (sub-study) Five 6ml EDTA samples for research: 30 mls

* Smear test and HPV testing: One liquid based cervical cytology

* Urine: (sub-study) One universal container

Total samples at Visit 3 (if applicable):

* Blood: One 6ml Red top tube: 6ml

* Blood: (sub-study) Five 6ml EDTA samples for research: 30 mls

All samples will be sent under the unique study number: cohort 1: SHiP/1/000/0, cohort 2: SHiP/2/000/0

8. DEFINITION OF END OF PROGRAMME

The end of the study is the date of final follow up of the final participant be that colposcopy or final smear results visit. The final results of the study will be shared with all participants as a letter and information sheet with explanation. A specific results-sharing participant meeting will be organised to allow further study results to be explained as required.

9. STATISTICAL ANALYSIS

- **Summarising data:** Characteristics of the study population will be described using mean and standard deviation, median and interquartile range, or number and percentage as appropriate. This information will also be stratified by age group.
- **Primary outcome:** The prevalence of cervical abnormalities within the cohort and by age group (18-24 and ≥25) will be calculated
- **Secondary outcomes:**
    - The prevalence of hr-HPV by type in young women with PaHIV will be calculated and stratified by age group
    - The prevalence of CIN2+ in young women with PaHIV will be calculated and stratified by age group
    - Comparison of HPV positivity with cervical abnormalities in young women with PaHIV
    - Characterisation of immunological and other correlates with hr-HPV carriage, cervical cytology results, CIN2+ and HPV type-specific antibody titres using the appropriate statistical test (Pearson's chi squared, Fisher's exact, Wilcoxon rank sum)
    - A measurement of HPV type-specific antibody titres in HPV vaccinated and unvaccinated young women with PaHIV, and a comparison with e.g. antibody titres to hepatitis B vaccination
    - Correlations of HPV-antibody titres and current immune function (CD4 count) and CD4 count at the time of vaccination
    - Acceptability will be assessed by the proportion of women who are offered enhanced cervical screening but decline.
    - Cost effectiveness will be assessed by evaluating the yield of abnormal results (cytology and hr-HPV) versus the cost of the tests

10. DATA MANAGEMENT

10.1 Access to data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with UK GCP and GDPR regulations.

10.2 Data recording and record keeping

a) CRF

The demographic and clinical data will be collected in the study CRF. Any relevant hard copies of source data will be filed locally under patients' unique identifier in accordance with Data Protection Act agreed practice. In all locations, any hard copy patient data will be stored in locked, filing cabinets with access restricted to pre-specified essential users.

b) Confidentiality

Information related to participants should be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

c) Record Retention and Archiving

The investigator will retain essential documents for 10 years as per Imperial College London policy (the sponsor). This includes subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study). Documents will be stored in such a way that they can be accessed/data retrieved at a later date. Consideration will be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

11. QUALITY ASSURANCE PROCEDURES

The study may be monitored, by the study sponsor, or audited in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

12. ADVERSE EVENTS

12.1 Definitions

(a) Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

(b) Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- Requires hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

12.2 Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

(a) Non serious AEs

All such events, whether expected or not, should be recorded.

(b) Serious AEs

A SAE form should be completed and sent to the Chief Investigator within 24 hours.

All SAEs should be reported to the Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs:

jrco@imperial.ac.uk

Chief Investigator email Tamara Elliott, tamara.elliott@nhs.net

13. ETHICAL AND REGULATORY CONSIDERATIONS

Ethics approval will be sought through the Research Ethics Committee and Health Research Authority.

(i) Initial Approval

Prior to the enrolment of participants, the IEC/IRB must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet and Consent Form, any other written information that will be provided to the participants.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the IEC/IRB for approval as instructed by the Sponsor. Amendments requiring IEC/IRB approval may be implemented only after a copy of the IEC/IRB's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or IEC/IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

14. DECLARATION OF HELSINKI

The study will be conducted in accordance with the principles of the Declaration of Helsinki.

15. GOOD CLINICAL PRACTICE

The study will be conducted in accordance with relevant regulations and with Good Clinical Practice, and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Human Tissues Act 2004.

The protocol, informed consent form and participant information sheet will be submitted to an appropriate REC and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16. REPORTING

An End of Study notification and final report will be submitted to REC, host organisation and Sponsor. Main laboratory research outcomes will be reported to the study participants in aggregate prior to public presentation of the study data.

17. PARTICIPANT CONFIDENTIALITY

The study staff will ensure that the participants' anonymity is maintained at all times. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

18. EXPENSES AND BENEFITS

Participants will be financially reimbursed for their participation in the study:

- Cohort 1: £20
- Cohort 2: £10

19. OTHER ETHICAL CONSIDERATIONS

We are offering cervical cytology examination outside the current age range recommended by NHS England. The research question is to explore the value of doing this amongst women with PaHIV, a unique cohort of high-risk individuals.

A potential ethical risk is that participants feel obligated to enrol in the study. This will be mitigated through correct explanation of voluntary nature of both the cervical testing and blood sample donation.

Individuals consenting to donate cervical samples will be informed of results, and any abnormal results will be referred for colposcopy, and managed as clinically appropriate. This is not research but standard clinical care, although these tests are being offered to women at a younger age than current guidelines.

Counselling about the meaning of hr-HPV will be carefully given with information made available. The tests may lead to anxiety and concern about cancer and these will be dealt with as appropriate according to individual situations and careful counselling by expert gynaecology services.

A maximum of 30ml of additional research blood will be taken. The only side effect of having blood taken will be the chance of bruising or vasovagal/syncopal response for which procedures will be in place to minimize risk. Where possible blood will be taken in conjunction with routine clinic bloods.

20. FINANCE

The study sponsor is Imperial College London. The core costs will be covered by funding from Imperial Health Charity. Additional funding is being sought and will support future research costs if successful.

21. INSURANCE

NHS indemnity operates in respect of the clinical treatment which is provided. Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study

22. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

23. ADMINISTRATIVE MATTERS

23.1 Source data

Source Data will be patient medical records, laboratory reports and a short 1-page questionnaire.

23.2 Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

23.3 Electronic Recording of data

Source data will be entered and stored on an electronic database. This database will be held at Imperial College NHS Trust and will be password protected.

23.4 Study Management Structure

Study management Group: will oversee the day-to-day running of the trial and the members will be primarily the clinical and data management teams.

23.5 Quality Control and Quality Assurance

Quality Control will be performed according to Imperial Clinical Trials Unit internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

The results may be published or presented by the investigator(s), but the Sponsor will be given the opportunity to review and comment on any such results before any presentations or publications are produced.

Preparation of a manuscript for rapid publication will be the responsibility of the chief investigator. High priority will be given to this and it is anticipated that a report will be completed within two months of completion of the study.

24. RESULTS DISSEMINATION

When completed the results of the study will be shared with participants through a participant results summary information sheet given at their next clinic appointment and they will have the opportunity to ask questions relating to the study.

Data will be presented at conferences and National and international meetings as well as submitted for publication in open peer reviewed journals when appropriate.

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