A Study of Reduced Dosing of the Nonavalent HPV Vaccine in Women Living with HIV
(The NOVA-HIV Study)

Research Protocol

Oak Tree Site

TITLE	A Study of Reduced Dosing of the Nonavalent HPV Vaccine in Women Living with HIV
Abbreviated Title	The NOVA-HIV Study
Protocol Version Date	6 Oct 2023
Funding Agency	Canadian Institutes of Health Research (CIHR)
Study Principal Investigator	Deborah Money, MD Women's Health Research Institute (WHRI) B327-4500 Oak Street Vancouver, BC V6H 3N1 Tel: (604) 875-2212 Fax: (604) 875-3895
Study Coordinating Centre	University of British Columbia Reproductive Infectious Diseases Research Program

Study Sites and Investigators

Study Site	**Local Investigators**
Study Coordinating Centre	Elisabeth McClymont
Oak Tree Clinic, BC Women's Hospital	Deborah Money/Chelsea Elwood/ Alicia Hornsberger/Julie van Schalkwyk
McMaster University Hospital, Hamilton	Shariq Haider
Toronto General Hospital, Toronto	Sharon Walmsley
St. Michael's Hospital, Toronto	Mark Yudin
Health Sciences Centre, Winnipeg	Vanessa Poliquin
Centre Hospitalier Universitaire Sainte-Justine	Isabelle Boucoiran
Centre Hospitalier de l'Université de Montréal (CHUM), Montréal	Valerie Martel-Laferrière
McGill University Health Centre, Montréal	Marina Klein
Centre Hospitalier de l'Université Laval, Québec City	Marie-Louise Vachon
Regina Qu'Appelle Health Region, Regina, Saskatchewan	Alexander Wong

Additional Investigators/Collaborators

Gynaecological Oncology

Marette Lee	Dept of Obstetrics and Gynaecology, UBC, Vancouver BC
Dirk van Niekerk	BC Cancer Agency, Vancouver BC

Pediatrics

Jason Brophy	University of Ottawa, Ottawa

Infectious Disease

Catherine Hankins	McGill University Health Centre, Montréal
Mona Loutfy	Maple Leaf Medical Clinic, Toronto
Alicia Berard	Health Sciences Centre, Winnipeg

Vaccine Evaluation

Manish Sadarangani	Vaccine Evaluation Centre, Vancouver BC

Laboratory Expertise

Alberto Severini	National Microbiology Laboratory, Winnipeg
Suzanne Gibbons	National Microbiology Laboratory, Winnipeg
Mel Krajden	BC Centre for Disease Control, Vancouver BC

Statistical Analysis, Study Design and Population Health

Joel Singer	Canadian HIV Trials Network

TABLE OF CONTENTS

SUMMARY

Title

A Study of Reduced Dosing of the Nonavalent HPV Vaccine in Women Living with HIV

Study population

Women Living with HIV (WLWH) aged 18-45 from across Canada who have not previously received an HPV vaccine.

Objectives

Primary

Determine whether peak anti-HPV16/18 geometric mean titers (GMTs) to 2 doses of 9vHPV vaccine are non-inferior to peak anti-HPV16/18 GMTs to 3 doses at month 7.

Secondary

1) Compare the antibody persistence at month 24 between the routine and extended vaccine schedule; and
2) Elucidate the acceptability of HPV self-sampling among WLWH in Canada.

Exploratory

3) Determine whether peak anti-HPV6/11/31/33/45/52/58 GMTs from 2 doses of 9vHPV vaccine are non-inferior to those from 3 doses at month 7;
4) Assess peak anti-HPV16/18 GMTs to 1 dose at month 1;
5) Describe the incidence, type, and severity of adverse events in WLWH; and
6) Elucidate the efficacy of 9vHPV vaccination up to month 24 (via persistent HPV infection with 9vHPV types, and cytological and histological HSIL).
7) Engage in a BC Cancer Registry linkage to investigate rates of pre-cancer or cancer diagnoses.
8) Investigate the role of viral and bacterial co-infection in the development of cervical dysplasia and vaccine breakthrough HPV infection in WLWH
9) Assess the uptake of HPV vaccination in WLWH aged 18-45 across Canada prior to study.

Timeline

First Visit, First Participant (FVFP): January 2023
Last Visit, Last Participant (LVLP): January 2027

Study design

This randomized clinical trial will enroll WLWH aged 18-45 from across Canada who have not previously received an HPV vaccine. Participants will be randomized 1:1 to receive 3 doses of 9vHPV vaccine at the routine vaccine schedule of 0/2/6 months or an expanded schedule of 0/6/12 months.

Inclusion Criteria

- Has a confirmed diagnosis of HIV infection
- Has a cervix (not have had their uterus removed)

- Age 18-45 years
- Not pregnant, and not trying to become pregnant
- Able to communicate in English if adequate translation is not available

Exclusion Criteria

- Unable to give fully informed consent
- Allergy to the vaccine or its components
- Prior receipt of any HPV vaccine.

Duration of study for each participant

24 months.

Three doses of 9vHPV vaccine will be given at 0/2/6 months in the routine interval group or at 0/6/12 months in the extended interval group. The primary endpoint occurs at month 7, prior to completion of all doses in the extended interval group.

1.0 **BACKGROUND**

Worldwide, cervical cancer is the 4th leading cause of cancer-related death in all women.[a] In many low and middle-income countries, it is the #1 cause of cancer-related death in women.[1] As such, in 2018 the World Health Organization (WHO) announced a **global call to action towards elimination of cervical cancer**, which Canada has committed to support.[2]

Given the high burden of cervical cancer (500,000 diagnoses and 300,000 deaths per year), achievement of the WHO's ambitious elimination goal will require new approaches and a deeper understanding of at-risk populations, including the nearly 18 million women living with HIV (WLWH) globally. In countries where cervical screening programs are well established, deaths still occur: for example, in Canada, one woman dies every day from cervical cancer (>400 women/year).[3] Cervical cancer disproportionately affects marginalized populations, particularly indigenous women, immigrant women, and WLWH who have a five-fold higher rate of cervical cancer.[3-5] **These disparities underscore the need to develop and evaluate population-specific preventative options towards global elimination of cervical cancer.**

The overlap in burden between HIV and cervical cancer is astounding. Around the world, ~38 million people—including ~63,000 in Canada—are living with HIV.[6, 7] Globally, there are ~6,000 new cases of HIV each week among young women (age 15-24y); in Canada, there are >2,500 new cases, >600 among women, each year.[7] Virtually all cervical cancer is caused by human papillomavirus (HPV) with 70% of cervical cancers being caused by the HPV types 16 and 18. HPV is the most common sexually transmitted infection, which infects ~80% of sexually active individuals at least once in their lifetime.[8] WLWH are more vulnerable to HPV persistence, and so have significantly higher rates of genital warts and cervical precancer/cancer.[5, 9] In North America, WLWH have twice the prevalence of HPV infection and 4-fold higher rates of invasive cervical cancer (26 vs. 6 per 100 000 person-years), compared to women without HIV.[10, 11] This high disease burden in WLWH is exacerbated in HIV-endemic regions worldwide where screening programs are often not present or woefully inadequate.[12]

Given the substantive achievement of development of HPV vaccines, one would have thought that the problem of cervical cancer would have been eliminated. However, although all licensed HPV vaccines have demonstrated remarkable safety, immunogenicity, and efficacy profiles in girls and women without HIV,[13] data is limited in WLWH, many countries have been unable to achieve comprehensive implementation, and catch up programs are rare beyond adolescent ages.[14, 15] Implementation of three-dose HPV vaccine programs for general populations began in 2006 and have moved in recent years to modified dose schedules; two doses are recommended by the WHO, and one dose has now been introduced at a population level in the UK due to cost savings and non-inferiority to three doses.[16, 17] Unique conditions of variable immune response to vaccination in WLWH require the generation of data specific to this population. Studies, including our own, have shown promising safety and immunogenicity in WLWH with 3 doses of older generation HPV vaccines.[18-20] Yet, there is only one publication, limited to only 100 individuals, on the currently used nonavalent HPV (9vHPV) vaccine in people living with HIV to date, leaving an important knowledge gap that must be addressed.[21] A strong understanding of 9vHPV vaccination in the large

[a] *Throughout this document the term 'women' is intended to be inclusive of all persons who were birth-assigned female regardless of their gender identity*

global population of WLWH that includes the assessment of novel approaches such as two-dose extended intervals can propel progress towards cervical cancer elimination.

Therefore, the National Advisory Committee on Immunization has named evaluation of 9vHPV vaccines in immunocompromised populations as a research priority.[22] The evaluation must include assessment of reduced dose schedules for WLWH, which would greatly increase the feasibility of HPV vaccination for these women who are most in need of protection and are critical to achieving cervical cancer elimination within the target timeframe of the next 80 years.

With HIV seropositivity rates in some countries at ~25% and many countries with >1 million people living with HIV, the ability to reduce the vaccination schedule by 1 dose could have a substantial positive impact on program feasibility. For more countries to be able to adopt HPV vaccination programs, costs associated with such programs must be reduced. Hence, data to determine the immunogenicity and effectiveness of reduced dosing will inform Canadian and global public health recommendations as well as potentially provide support for reduced dose programming in high HIV seroprevalence low and middle-income countries, thereby accelerating global health equity.

The extended dosing interval allows us to assess peak antibody titers to 3 doses in the routine group at month 7 and peak antibody titers to 2 doses in the extended group at month 7, while still offering the current 3-dose standard of care to all WLWH in the study. It is standard in vaccine research to use the "peak" antibody titer (i.e., titer at 1 month post vaccination) as a primary immunologic endpoint demonstrating overall maximal immunologic response. This endpoint is also the basis of licensure for many vaccines and would be necessary and sufficient for regulators to change the recommended use of a vaccine. Indeed, the approval of reduced 2 dose HPV vaccine schedules in the general population was based on immunobridging data of the peak antibody titers.[23, 24]

2.0 HYPOTHESIS

We hypothesize that the peak anti-HPV16/18 antibody titer (measured by geometric mean titer; GMT) after 2 doses of 9vHPV vaccine will be non-inferior to peak anti-HPV16/18 antibody titer after 3 doses.

3.0 OBJECTIVES

The overall goal of the study is to assess whether 2 doses of vaccine are non-inferior to 3 doses. Participants will be randomized 1:1 to receive 3 doses of 9vHPV vaccine at the routine vaccine schedule of 0/2/6 months or at an extended schedule of 0/6/12 months.

1. **Primary Objective**
   1) Determine whether peak anti-HPV16/18 geometric mean titers (GMTs) to 2 doses of 9vHPV vaccine are non-inferior to peak anti-HPV16/18 GMTs to 3 doses at month 7.

2. **Secondary Objectives**
   2) Compare the antibody persistence at month 24 between the routine and extended vaccine schedule.
   3) Elucidate the acceptability of HPV self-sampling among WLWH in Canada.

3. Exploratory Objectives

4) Determine whether peak anti-HPV6/11/31/33/45/52/58 GMTs from 2 doses of 9vHPV vaccine are non-inferior to those from 3 doses at month 7.
5) Assess peak anti-HPV16/18 GMTs to 1 dose at month 1.
6) Describe the incidence, type, and severity of adverse events in WLWH.
7) Elucidate the efficacy of 9vHPV vaccination up to month 24 (via persistent HPV infection with 9vHPV types, and cytological and histological HSIL).
8) Engage in a BC Cancer Registry linkage to investigate rates of pre-cancer or cancer diagnoses.
9) Investigate the role of viral and bacterial co-infection in the development of cervical dysplasia and vaccine breakthrough HPV infection in WLWH
10) Assess the uptake of HPV vaccination in WLWH aged 18-45 across Canada prior to study.

4.0 STUDY DESIGN

1. Design

The trial is a multicenter, observer-blind, randomized, phase IV clinical trial. All lab personnel assessing the primary endpoints are blinded to group allocation. For further details on observer blinding and randomization, please see section 5.2. Study sites are located in Vancouver, Regina, Winnipeg, Toronto, Hamilton, Montreal, and Quebec City.

2. Rationale

HPV vaccination has transformed the cervical cancer landscape, but current adolescent HPV vaccine programs alone will lead, at best, to elimination of cervical cancer in 80 years.[28] Reduction of disease burden and deaths requires more rapid elimination through: (i) scale up of screening and treatment and (ii) vaccine programs beyond adolescent-based models to prioritize additional age groups and key populations.[29]

For persons who are immunocompromised, we do not have sufficient data on how to deploy HPV vaccines. WLWH are especially vulnerable; they are often marginalized and are least likely to engage in screening programs.[30] Importantly, HIV is a major global contributor to HPV incidence and cervical cancer development, resulting in significantly higher rates of disease among the world's 17.8 million WLWH.[31] Therefore, global elimination strategies must include an evidence-based plan to immunize WLWH not only prior to sexual debut, but also across high-risk periods for HPV acquisition and into adulthood. Following the initial introduction of three-dose vaccine schedules, two-dose schedules have been adopted worldwide, based on robust studies conducted in immunocompetent girls and women,[23] and one-dose schedules are now being considered and recommended in some countries for the general population.[17] However, it is still recommended that WLWH obtain 3 doses of vaccine due to a lack of data to support reduced dosing in this population.[22, 32] This requirement of additional doses reduces the feasibility of vaccination for many women as well as the financial and logistic feasibility of vaccine programs in HIV-endemic countries.[33]

5.0 STUDY COHORT

1. Population

Recruitment of 450 WLWH aged 18-45 years is being performed by research staff at 10 sites across Canada. The 450 WLWH will be randomized 1:1 to two groups:

1) Three doses of 9vHPV vaccine at the routine dosing schedule of 0/2/6 months.

2) Three doses of 9vHPV vaccine at an extended dosing schedule of 0/6/12 months.

Inclusion Criteria

- Has a confirmed diagnosis of HIV infection
- Has a cervix (not have had their uterus removed)
- Age 18-45 years
- Not pregnant, and not trying to become pregnant
- Able to communicate in English if adequate translation is not available

Exclusion Criteria

- Unable to give fully informed consent
- Allergy to the vaccine or its components
- Prior receipt of any HPV vaccine.

Females aged <18 are excluded because all children, including those with HIV, are vaccinated in adolescent programs in Canada leaving very few eligible under that age. Further, we seek to inform the use of 9vHPV vaccine beyond adolescent program ages. The upper age limit of 45 years was chosen based on vaccine licensure as the 9vHPV vaccine is currently authorized for use in females ages 9-45.

Women will not be excluded based on baseline HPV immune status. All women can benefit from vaccination as they are virtually all seronegative for at least one 9vHPV type. Also, HPV seronegativity is not required for vaccination programs, thereby making our findings most relevant to vaccination programs, which would be conducted without a seronegativity requirement. We will assess baseline HPV immune status for use in post hoc outcomes analysis.

2. Randomization

Randomization will be stratified by site using permuted blocks of random size. A CIHR Canadian HIV Trials Network (CTN) statistician will computer-generate random allocations, which will be uploaded to a password-protected webpage. When an eligible consenting participant is identified, the webpage will issue a study identification number and vaccine regimen allocation. An automated audit trail will track date and time of transactions along with study identification number, stratum, and allocation. No placebo will be used as the primary aim of this study is to assess non-inferiority to different 9vHPV vaccine dosing regimens, not to compare outcomes to unvaccinated women.

Randomization of participants to the two groups of the trial will prevent selection bias in group assignment and improve balance between groups with respect to known (e.g. HIV viral load suppression) and unknown variables of importance.

The primary endpoint of this trial and most other endpoints relate to the anti-HPV immune response. All lab personnel assessing these immune endpoints will be blinded to the group allocation. Observer blinding is appropriate as participants and field staff cannot be blinded to the dosing interval and participants and field staff are unable to modify immune endpoints.

6.0 STUDY CONDUCT

1. Adherence to Industry Guideline and Regulations

This trial is to be conducted in accordance with the protocol, ICH GCP, and Health Canada Food & Drug Regulations, Part C Division 5. All study staff should be familiar with the following documents:

- ICH GCP: http://www.ich.org/cache/compo/276-254-1.html
- Food and Drug Regulations, Part C Division 5: https://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/page-85.html#h-577812

All investigators and their investigative sites are obligated to comply with investigator responsibilities, monitoring, and archiving data, audits, confidentiality, and publication requirements.

The Study Coordinating Centre shall also accept the responsibilities of the Sponsor as outlined in ICH GCP.

2. Research Ethics Board (REB)

Each site will be required to utilize a REB that conforms to section 3 of the GCPs: 3.1 Responsibilities, 3.2 Composition, Functions and Operations, 3.3 Procedures, 3.4 Records.

Prior to the conduct of this trial, the protocol, consent form, and all related documents must be submitted to the REB at each site. Approval for this study must be granted before the trial can be started at that site.

The Principal Investigator at each site will forward a copy of the REB approval to the Study Coordinating Centre before the first participant is enrolled in the study at that site. All amendments to the protocol that affect the safety and/or welfare of the study participants shall be submitted to the site REB and approved prior to implementation.

All study staff should be familiar with the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans: https://ethics.gc.ca/eng/documents/tcps2-2018-en-interactive-final.pdf

3. Informed Consent

Each participant or their parent/legally authorized representative (if applicable) must participate in the informed consent process and sign and date the informed consent form before any procedures specific to this protocol are performed on that participant. In the absence of a site SOP for informed consent, the site will write a note to file explaining the procedures followed while obtaining informed consent/assent. Each site will have the option to participate in the informed consent process in either French or English. For sites

where translation services are available and accessible throughout the course of the study, participants who do not speak English or French are welcome to enroll.

At each subsequent study visit, participants and their parent/legally authorized representative (if applicable) will be asked if they wish to continue in the study and give their ongoing consent to participate.

Study consent and assent forms must be approved by a REB at the particular study site. Informed consent form templates are included in the protocol appendices and may be amended as per site and REB requirements. REB approved consent forms for each site are to be sent to the Study Coordinating Centre and updated as necessary.

6.3.1 **Capacity to Consent**

The NOVA Study will be enrolling participants between ages 18 and 45. The Capacity to Consent steps below apply to potential participants below the age of majority in their respective province.

After reviewing the consent with the minor, the trial coordinator will assess the minor's understanding of the study by asking them:

1. To explain what they understand about the purpose of the study
2. If they remember approximately how long it will take to complete study visits
3. If they remember what types of samples may be collected at the study visits
4. If they understand one way that that their privacy will be protected, (i.e. that unique identifiers will be used on study samples and documents, secure storage etc.)
5. If they understand how much they will be reimbursed for participation in the study
6. If they are aware that they can withdraw from the study at any time
7. If they can point out in the consent form the phone number that could be used to reach the study investigator if they have questions
8. If they understand that the linkage to their provincial cancer registry, and subsequent collection of first name, last name, data of birth, and PHN collected for this purpose is optional.

The trial coordinator will determine that the minor has the capacity to consent if they are able to satisfactorily respond to the above questions and will document whether responses were satisfactory or not. If the minor is not able to respond to the questions in a satisfactory manner, they will be deemed as not having the capacity to consent, the consent process will be halted and the minor will not be offered participation in the study.

4. **Source Documentation**

A screening log will be kept by each study site, in order to track how many potential participants were approached, how many were not eligible due to having already received an HPV vaccine, and also those who decline participation.

Following collection of informed consent, limited study source documentation should be kept for each participant at the study site. Source data is raw data such as documentation of original observations and activities. Source data is the first time and place an observation is documented, for example the documentation of a urine pregnancy test.

Study source documentation should be captured separately in the participant study chart; however, when the original source data is such that it cannot be placed with the participant source document chart, for example, the source data is contained in the hospital patient chart, sites can note where in the electronic chart this was documented from.

A source document template will be provided to sites by the Study Coordinating Centre. However, sites are not required to use the template if other approved methods of capturing source data are preferred. Alternate methods of capturing source data must be approved by the Study Coordinating Centre.

5. Monitoring

The sites will be remotely monitored to ensure that the trial is being conducted in accordance with the protocol, ICH GCP, and Health Canada Food & Drug Regulations, Part C Division 5.

Consent documentation will be reviewed at 100%. Source documentation/CRF reconciliation will occur at 20% at each site. Monitoring at each site will be based on enrollment at that site and will occur remotely with option for in person monitoring should this be required based on issues identified. A close-out of the study will occur after the Last Participant Last Visit has been conducted at each site.

Enrollment and study progress reports will be requested of the study sites at a frequency to be determined by enrollment rates.

7.0 STUDY PROTOCOL

1. Participant Identification Number (PID#) Assignment

Participant identification numbers will be assigned sequentially to each person consented for participation in the study. The participant number will be assigned as follows: 2-digit site number (See Table 7.1.1) followed by a three-digit participant number. For example, the first participant consented to the study at the Oak Tree Clinic will be assigned the number 01001. All participants will have a 5-digit participant identification number. A participant enrollment log will be provided to each site. This log should capture all participants consented and for who a PID# has been assigned. PID# are not to be used more than once. The PID will be used for identification of participants in the source document study chart, CRFs, and laboratory specimens. It will be through these unique identifiers that participant data and laboratory samples leaving the individual study sites will be identified and tracked.

_____ _____ _____ _____ _____
(site number) (participant number)

7.1.1 Table of Site Numbers

Site Number	Study Site
01	Oak Tree Clinic - Children and Women's Health Centre of BC, Vancouver
02	Health Sciences Centre, Winnipeg
03	Toronto General Hospital, Toronto
04	St. Michael's Hospital, Toronto
05	McMaster University Hospital, Hamilton
06	McGill University Health Centre, Montreal
07	CHU Sainte Justine, Montréal
08	Centre Hospitalier de l'Université Laval, Québec City
09	Centre Hospitalier de l'Université de Montréal (CHUM), Montréal
10	Regina Qu'Appelle Health Region, Regina

2. Considerations for Special Groups

7.2.1 Suspension of Study Procedures in Pregnancy

In the event of a pregnancy during the study, the investigative site is to notify Dr. Deborah Money at the Study Coordinating Centre using a pregnancy reporting form as soon as the investigative site is made aware of the pregnancy. Following the resolution of the pregnancy, the investigative site will provide an update to the Pregnancy Reporting Form and inform the Study Coordinating Centre.

Study vaccination is to be suspended in pregnant participants and may be resumed at the resolution of pregnancy. All other study procedures may continue.

If a participant has a positive pregnancy test as part of the study visit, the clinic doctors or nurses will be notified and they will let the participant know about the result. If the participant receives a positive test outside of the clinic, they are asked to let the team know. Following the diagnosis of pregnancy, study vaccination will be temporarily stopped, and participants will be invited to resume vaccination at the same point that it was stopped, 1 month after the conclusion of the pregnancy if they choose to do so.

Pregnant participants will be invited to sign a Pregnancy Consent Form.

Information to be collected following signing of the Pregnancy Consent includes:

- estimated date of delivery
- the outcome and mode of delivery
- any important diagnoses associated with the pregnancy and delivery
- the date of birth or pregnancy loss
- the gestational weeks at birth or pregnancy loss
- infant's sex and weight
- infant's APGAR scores

- if the infant was required to stay in hospital longer than usual, and if so, what the cause was

3. Summary of Study Visits

Table 1A. Schedule of Visits (Routine Group: Follows Routine Vaccine Schedule)

	Informed Consent	Pregnancy Test	9vHPV Vaccine	Blood Draw	HPV DNA Swab [a]	AE Assessment	Ongoing Medical History	HPV Self-Sampling Questionnaire
Month 0	X	X	X	X[c]	X	X	X	X[b]
Month 1				X		X	X	
Month 2		X	X			X	X	
Month 6		X	X		X	X	X	
Month 7				X		X	X	
Month 12					X	X	X	
Month 24				X	X	X	X	X

[a] Self-sampling where acceptable to participant, [b] Pre-HPV-swabs, [c] Pre-vaccination

Table 1B. Schedule of Visits (Extended Group: Follows Extended Vaccine Schedule)

	Informed Consent	Pregnancy Test	9vHPV Vaccine	Blood Draw	HPV DNA Swab [a]	AE Assessment	Ongoing Medical History	HPV Self-Sampling Questionnaire
Month 0	X	X	X	X[c]	X	X	X	X[b]
Month 1				X		X	X	
Month 2								
Month 6		X	X	X[c]	X	X	X	
Month 7				X		X	X	
Month 12		X	X		X	X	X	
Month 24				X	X	X	X	X

[a] Self-sampling where acceptable to participant, [b] Pre-HPV-swabs, [c] Pre-vaccination

4. Study Visits

7.4.1 Study Treatments

Each participant will be followed for a duration of 24 months. Study visits will take place at the site from which each participant is enrolled. Routine clinical exams and blood work will be done as indicated for clinical care with results documented for the study, as appropriate. Participants will be randomly assigned 1:1 to one of two research groups. The Routine Group will have 7 study visits over 2 years at the clinic. The Extended Group will have 6 study visits over 2 years at the clinic.

- **ROUTINE GROUP**: The routine group will receive the HPV vaccine (GARDASIL®9) at the routine vaccine schedule of three doses given at month 0, month 2, and month 6.

- **EXTENDED GROUP**: The extended group will receive the HPV vaccine (GARDASIL®9) at an extended vaccine schedule of three doses given at month 0, month 6, and month 12.

7.4.2 Study Duration

The primary endpoint occurs at month 7 prior to completion of all doses in the extended interval group. All additional endpoints beyond month 7 are based on completion of the three doses and will provide critically-needed data on extended dosing intervals, HPV self-sampling acceptability, safety, and efficacy of 9vHPV vaccines in WLWH for whom the data is currently extremely limited. The 24-month follow-up duration will allow us to map immune titer dynamics to the vaccine out to the expected plateau in immunocompetent populations based on our prior data from WLWH (data not published) as well as the general population.[34, 35]

7.4.3 Timing of Study Visits

Where possible, study visits will be scheduled on the same day as the participant's routine clinic visits for HIV care.

7.4.4 Delays and Contraindications to Study Procedures

7.4.4.1 Indications for a Delay in Vaccination

Vaccination may occur after the following condition has resolved and no other exclusion criteria are met.

- Current febrile illness or oral temperature over 38.5C
- Moderate to severe illness within 24 hours of study vaccine administration
- Vaccinations will be suspended in pregnant women and may resume following the resolution of the pregnancy
- Administration of immunoglobulins and/or any blood products within 30 days of a vaccination
- Any live virus vaccines given within 28 days of vaccination.
- Inactivated or recombinant vaccines (e. Influenza, Hep B, Tdap, Men C, COVID-19) may be given up to 8 days before a study HPV vaccination or at least 8 days following the study vaccine

Exceptions may be made under exceptional circumstances, for instance if a participant is from out of town and additional travel to the site for additional vaccination (eg. Influenza vaccine) would prove very difficult. In this case, document the additional vaccines clearly in the source documents and indicate the date given

7.4.4.2 Indications for a Delay in Vaginal Swab Sampling

- Self-obtained samples may continue to be collected during pregnancy.

- Participants must not be menstruating at the time of the vaginal swabbing. The participant may have all other study procedures performed. The participant will be invited to take the swabs home to self-collect when they are not menstruating with instructions on how to return the swabs to the study centre.

7.4.4.3 Indications for a Delay in Study Blood Sampling

- Administration of immunoglobulins and/or any blood products within 30 days of study blood sampling
- Administration of any live virus vaccines given with 28 days of a blood sample
- Administration of inactivated or recombinant vaccines (e.g. Influenza, Hep B, Tdap, COVID) up to 8 days before study blood sample collection is acceptable

7.4.4.4 Contraindication for Continuation of Study Procedures

- Withdrawal from the study
- Anaphylactic reaction to HPV vaccine related component
- Development of any newly confirmed or suspected immunosuppressive or immunodeficient condition (other than HIV/AIDS)
- Administration of any HPV vaccine not provided as part of the study
- Investigator decides it is not in participant's best interest
- Participant decides to discontinue vaccine series

7.4.5 Outline of Study Visits

Month 0

At the Month 0 visit, the following will be done:

- Collection of informed consent.
- Baseline information will be recorded including information such as: general health history, HIV history and medication history, current antiretroviral medications
- A brief physical assessment (temperature, height, weight).
- Regular clinic and study bloodwork.
- A urine pregnancy test (regardless of age or sexual activity).
- A short questionnaire regarding how the participant feels about self-collecting a vaginal swab for the purpose of HPV screening for cervical cancer.
- A self-collected vaginal swab for detection of HPV DNA, and a retention swab.
- The first of three HPV vaccine doses will be given.
- Instructions regarding the 14-Day Post-Vaccine Symptom Diary

Month 1

At the month 1 visit the following will be done:

- Assess ongoing consent.
- Review of any changes in health status and/or medications.
- Review of all adverse events occurring in the first 14 days following vaccination and any significant adverse events following this period.
- Study bloodwork.

Month 2

This visit will only occur in participants in the routine group.

At the month 2 visit, the following will be done:

- Assess ongoing consent.
- A brief assessment of vaccine contraindications (including temperature).
- A urine pregnancy test (regardless of age or sexual activity).
- Review of any changes in health status and/or medications.
- Review of any significant adverse events last study visit.
- The second of three HPV vaccine doses will be given.
- Instructions regarding the 14-Day Post-Vaccine Symptom Diary
- PLEASE NOTE: there will be no blood drawn at this visit.

4 weeks after the Month 2 visit, the study coordinator will contact the participant to review any adverse events occurring in the first 14 days following vaccination and any significant adverse events following this period. This will act as a safety follow-up, as participants will not be seen in-person again until Month 6.

Month 6

At the month 6 visit the following will be done:

- Assess ongoing consent.
- A brief assessment of vaccine contraindications (including temperature).
- A urine pregnancy test (for all participants regardless of age or sexual activity).
- Review of any changes in health status and/or medications.
- Review of any significant adverse events following this period.
- An HPV vaccine dose will be given (for the routine group, this will be the 3rd and final dose; for the extended group, this will be the 2nd dose).
- Instructions regarding the 14-Day Post-Vaccine Symptom Diary
- A self-collected vaginal swab for detection of HPV DNA, and a retention swab.
- PLEASE NOTE: there will be no blood drawn at this visit for the routine group; study bloodwork will be done for the extended group.

Month 7

At the month 7 visit the following will be done:

- Assess ongoing consent.
- Review of any changes in health status and/or medication.
- Review of all adverse events occurring in the first 14 days following vaccination and any significant adverse events following this period.
- Study bloodwork.

Month 12

At the month 12 visit, the following will be done in participants from the routine group:

- Assess ongoing consent.
- Review of any adverse events since last study visit.
- A brief physical assessment (weight).
- A review of any changes in health status and/or medications.
- A self-collected vaginal swab for detection of HPV DNA, and a retention swab.
- PLEASE NOTE: there will be no blood drawn at this visit.

At the month 12 visit, the following will be done in participants from the extended group:

- Assess ongoing consent.
- A brief physical assessment (weight).
- A urine pregnancy test (regardless of age or sexual activity).
- A brief assessment of vaccine contraindications (including temperature).
- Review of any changes in health status and/or medications.
- Review of any significant adverse events since vaccination.
- A self-collected vaginal swab for detection of HPV DNA, and a retention swab.
- The third of three HPV vaccine doses will be given.
- Instructions regarding the 14-Day Post-Vaccine Symptom Diary
- PLEASE NOTE: there will be no blood drawn at this visit.

4 weeks after the Month 12 visit, the study coordinator will contact the extended group to review any adverse events occurring in the first 14 days following vaccination and any significant adverse events following this period. This will be act as a safety follow-up, as participants will not be seen in-person again until Month 24.

Month 24

At the month 24 visit, the following will be done:

- Assess ongoing consent.
- Review of any significant adverse events since last study visit
- A review of any changes in health status and/or medication.
- A short questionnaire regarding how the participant feels about self-collecting a vaginal swab for the purpose of HPV screening for cervical cancer.
- A self-collected vaginal swab for detection of HPV DNA, and a retention swab.
- Study bloodwork.

5. Study Procedures in Detail

7.5.1 Informed Consent

Please refer to section 6.3 for detailed information on Informed Consent.

7.5.2 Medical History

General Medical Systems History

A pre-existing health history including current medications will be collected at the first visit to ascertain a baseline prior to vaccination. The health history and medications/exposures will be updated at each subsequent visit. The baseline health assessment will be sufficiently detailed to confirm eligibility to participate and to identify a baseline for appropriate management of any SAEs that are reported.

Focused Medical History:

HIV diagnosis date & mode of acquisition if known; current HIV treatment, abnormal Pap tests, colposcopies, and treatments; history of genital warts and treatments; STIs; reproductive history will be ascertained at the Month 0 visit and updated at subsequent visits.

Please ensure at the comprehensive medical history is taken and documented prior to vaccination.

7.5.3 Brief Physical Assessment

The brief physical assessment will include: height (month 0 only), weight (month 0 and month 12 only), and temperature. Temperature should be assessed prior to each vaccination.

7.5.4 Clinical Laboratory Investigations

Clinical blood samples will be collected, handled, processed, and analyzed at site local laboratories as per local practices. Current HIV and general health status will be determined by abstraction of clinical chart data and routine clinical laboratory tests (CBC, liver enzymes, renal function, CD4 T cell subsets, and HIV RNA quantitative PCR [viral load]).

7.5.5 Study Blood Work

Ensure all blood tubes are clearly labeled with the 5-digit PID#, collection date, and visit number. Study blood work must be collected within 24 hours of the study self-collected HPV DNA sample. For complete serology sample protocol, see Laboratory Protocol.

7.5.5.1 Serum Antibody Testing

Whole blood by venous route is to be collected observing aseptic conditions into one 10mL red top Serum Vacutainer (non-heparinized, non-EDTA, non-serum separator) tube. Specimens should be placed upright and allowed to clot for 30 to 60 minutes. After the sample has clotted is should then be

refrigerated at 2-8 degrees Celsius until centrifuged. Samples are to be centrifuged within 24 hours of collection and according to manufactures specification to allow for complete separation of serum. Serum is to be aliquoted using a plastic pipette into 2 cryovials, each containing a minimum of 2.0 mL and then frozen between -60 and -80 degrees Celsius at the investigative site until recalled by the Study Coordinating Centre. One aliquot will go to the BC Women's Research Lab (Women's Health Research Institute) for storage, and the other will be transferred to the Merck Laboratory for in-house serotesting. There, serum anti-HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 immunoglobulin levels will be measured using competitive Luminex immunoassay (cLIA).

7.5.5.2 **Immune Response Sub-Analysis**

Peripheral blood mononuclear cells (PBMCs) will be collected at month 0 and month 7 from a subset of 60 participants in each arm of the trial (120 participants total) for future exploration of the nature of the immune response in women with and without HIV viral load suppression (funding for sample analysis to be applied for in future). 30mls of whole blood by venous route is to be collected observing aseptic conditions into three 10mL heparin tubes.

7.5.6 **βHCG Pregnancy Test**

All participants are to provide a fresh urine sample for a dipstick pregnancy test at the first visit and before (same day) the administration of each of the 3 doses of the HPV vaccine. Results of the urine dipstick test must be available and negative prior to proceeding with the vaccination. Alternatively, a negative serum pregnancy test result done the day of the vaccination is acceptable.

Participants will be provided with counseling regarding avoidance of pregnancy. Effective birth control measures for this study are to include: birth control pill, IUD, Depo Provera, hormonal implants, male or female condom with or without spermicide, diaphragm or sponge with or without spermicide, or abstinence.

7.5.7 **HPV Self-Sampling Questionnaires**

Questionnaires elucidating attitudes towards HPV self-sampling will be administered at the Month 0 visit and at study end to explore attitudes towards HPV self-sampling before and after using this testing methodology within the study. The survey will assess attitudes regarding acceptability, comfort, and willingness to use this sampling methodology in future.

7.5.8 **Self-Collected Vaginal Swab Samples**

Samples will be clearly labeled with the 5-digit PID#, collection date, and visit month. Ideally, HPV DNA samples should be collected within 24 hours of the study blood work sample. Samples should be stored at room temperature until received by the site laboratory.

Participants will be provided one dry swab and instructed how to self-collect a vaginal specimen using a standard script and diagram. Sample collection will occur in a private space within the clinic where the study visit is occurring and will be returned to study staff immediately. Participants will collect one sample for testing. An extra swab will be provided in case the original swab is dropped or damaged. The sample will be aliquoted into two vials (1 analysis sample, one retention sample). For full sample processing procedures, see Laboratory Protocol.

If the participant is menstruating at the time of their study visit, the swab collection will be re-scheduled for a later date or the participant will be invited to take the sample collection kit home to collect when not menstruating. Participants will be given instructions and postage paid mailing materials to return the swabs to the study centre. Participants will be given the option to have a physician or nurse practitioner collect the swabs for them if they do not wish to self-swab.

7.5.9 **Post-Vaccine Diaries**

Following their first, second, and third HPV vaccine doses, participants will be asked to complete a 14-day Post-Vaccine Symptom Diary. They will be instructed to fill out the diary with details regarding any symptoms that they experience following their vaccination. The diary may be offered in two formats: paper or a REDCap survey. If the diary is in paper format, participants will be provided with a stamped envelope to return it to the study site or they may bring it with them to their next study visit.

7.5.10 **Concomitant Medications and Exposures**

Concomitant medications for the purpose of this study, to be documented, are to include: antiretroviral therapy, other vaccines, prescriptions, over the counter medications, hormonal, herbal, vitamin, alternative and complementary therapy; exposures will include: use of drugs of addiction, tobacco, and alcohol.

At each visit, participants will be asked about their medication usage/exposures. All concomitant medications and exposures taken at any time during the period starting with the first visit will be collected. Information to be collected should include: name of medication (generic name or trade name for combination medications), medical indication, total daily dose, and route, start and stop dates. PRN medications may be listed as PRN for total daily dose.

If a participant is on and off a treatment throughout the study, please ensure that the start and stop date indicate the time the participant was on and off treatment. Additionally, if the dosages change a stop date should be entered for the previous dosage and a new entry made for the start of the new dosage.

For exposure to drugs of addiction, tobacco, and alcohol use, the most basic description, for example, THC, heroin, cocaine, tobacco, ETOH. For frequency, have the participant estimate usage per day, week, or month.

Participants' antiretroviral therapy use over the course of the study will also be captured.

7.5.11 **BC Cancer Registry Linkage**

For participants who provide specific consent, a linkage the BC Cancer Registry will be performed to determine pre-cancer or cancer diagnoses. First name, last name, full date of birth and PHN will be used for this linkage. This linkage may be done a number of years after the study is finished.

For sites that do not have a Provincial cancer registry, cancer outcomes may be obtained by clinical chart review.

The BCCDC Data Linkage and Destruction Plan, is as follows:

1. BCCDC Data Guardian creates a folder in \\Phsabc\root\BCCDC\Groups\public\DROPBOX
2. NOVA Team prepares the data set to be linked, encrypts dataset and shares to BCCDC via the above network folder
3. NOVA Team shares encryption password with designated BCCDC Data Guardian
4. Data Guardian adds the NOVA dataset to designated folder in the BCCDC Central Data Repository
5. Data Guardian unencrypts the NOVA dataset
6. Data Guardian links the NOVA dataset and BCCDC dataset using personal identifiers (PHN, DOB, name) to create Combined Dataset
7. Data Guardian replaces PHN with Study ID, removes DOB and name
8. Data Guardian encrypts de-identified Combined Dataset and shares with designated NOVA Researcher via the folder above
9. NOVA Researcher adds file to access limited dataset on the PHSA Network
10. NOVA Researcher confirms Combined Dataset is ok, notifies Data Guardian
11. Data Guardian destroys BCCDC and NOVA datasets

NOVA Researchers will retain de-identified combined dataset for 15 years post publication of data (in keeping with section 8.6.A of the application)

At or before 15 years after the end of the study, NOVA Researchers will destroy the dataset and notifies BCCDC and NOVA Teams of its destruction.

8.0 **HPV VACCINE ADMINISTRATION**

1. **Characteristics**

The vaccine to be used in this trial is GARDASIL®9. GARDASIL®9 (Nonavalent Human Papillomavirus [Types 6, 11, 16, 18, 31, 33, 45, 52, 58] Recombinant Vaccine) is a recombinant nonavalent vaccine that protects against HPV.

2. **Vaccine Acquisition**

Merck will provide commercially available lots of GARDASIL®9 to investigative sites following cold chain procedures. Where available, sites will use free, publicly-available GARDASIL®9 vaccines prior to the Merck lots.

3. Vaccine Storage

Vaccine will be stored at 2-8 degrees Celsius, do not freeze, and protect from light. The vaccine is to be stored in the local hospital pharmacy, or secure continuously monitored refrigerator accessible to study clinical staff. Demonstration of stable refrigeration temperatures for 1 week prior to vaccine storage in the designated study refrigerator is required. Ongoing documentation of adequate cold chain must be kept by each site.

4. Allocation

Supplied vaccine is open label.

5. Accountability

Vaccine accountability must be maintained throughout the clinical trial. All vaccines arriving at the site will be entered onto a vaccine accountability log provided by the Study Coordinating Centre. All vaccines used, wasted, replaced, expired, or destroyed is to be tracked on the accountability log.

6. Dosage and Administration

Doses are given at 0, 2 and 6 months (in the routine group), and 0, 6, and 12 months (in the extended group). Doses are to be given intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh. Injection should occur using a 22 or 23-gauge needle, one inch in length. The full recommended dose of 0.5ml must be used.

The vaccine made available for this study will be in single use vials. A separate sterile syringe and needle must be used for each individual. The vaccine should be used as supplied with no dilation or reconstitution necessary.

Prior to injection, the vaccine (vial/syringe) is to be thoroughly agitated immediately prior to administration to ensure suspension of the vaccine. The fluid should be white and cloudy after agitation. Inspect the fluid for particulate matter and discoloration prior to administration. Discard the vaccine if particulates are present or if it appears discolored and document on the vaccine accountability log.

Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile 22 or 23-gauge needle and syringe free of preservatives, antiseptics, and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded. Replace the needle for administration.

7. Documentation

Clinical staff will document the date, time, and location of vaccine administration in the Participant's clinical chart or electronic medical record. Clinical staff will also indicate whether the study vaccine or publicly available vaccine was given. Research staff will

transcribe this information into the study case report form. Ensure that the vaccine usage has been documented on the vaccine accountability log. Ensure clinical staff are aware that a participant has received a dose of vaccine for documentation in clinical records.

8. Replacement

Replacement of vaccine, if necessary, will be from open label stock. Documentation of wasted and replaced vaccine is necessary on the vaccine accountability log.

9.0 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Please ensure that a comprehensive medical history is taken and documented prior to vaccination to ensure that only new adverse events are captured as AEs.

1. Adverse Events

All adverse events will be collected during the vaccination phase of the study for up to 14 days following a vaccine. Documentation should include, diagnosis (or symptom if not diagnosed), start and stop dates, intensity (using the DAIDS AE grading table), and treatments. Narrative notes should detail the event and possible contributing factors. All AEs collected in the vaccination phase of the study (up to 14 days following a vaccine) must be assessed as to their relationship to the vaccine and signed off by a site investigator.

All newly diagnosed chronic illnesses; worsening, increase in severity, or frequency of pre-existing conditions; or medically significant illnesses occurring more than 14 days after the administration of the vaccine will be collected throughout the entire study as updates to the general medical history.

2. Serious Adverse Events

Serious adverse events (AEs), medically attended AEs, and provincially reportable AEs following immunization will be collected. Serious AEs will be defined per GCP-ICH guidance and all will be collected regardless of presumed relatedness and/or expectedness. AEs will be reviewed at each study visit, and participants will have emergency contact details for the local research team to report events between visits.

9.2.1 Definitions

A SAE is any untoward medical occurrence that:

- Results in death
- Is immediately life-threatening
- Requires inpatient or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect in the offspring of a study participant
- Other medical events that may not be immediately life-threatening, result in death or hospitalization but may be significant or jeopardize the participant or require medical or surgical intervention to prevent one of the defined

SAEs as an outcome
All SAEs will be recorded, regardless of time since vaccination.

9.2.2 Reporting Time Period

All SAEs occurring during the study must be recorded and reported to the Study Coordinating Centre whether or not they are considered vaccine-related. All SAEs are considered severe. The investigator must make a determination of causality using clinical judgment and after considering and investigating alternative causes such as underlying conditions, concomitant therapies, other risk factors and the temporal relationship.

SAE reports will be faxed to Dr. Deborah Money at the Study Coordinating Centre and the Canadian HIV Trials Network (CTN) within 24 hours of discovery or notification to the study centre of an SAE. Site investigators are obligated to notify their REB as per local reporting requirements.

SAE Notification:
Dr. Deborah Money (fax#) 604-875-3895 (24 hours)
AND CTN (fax#) 604-806-8005 (48 hours)

The Study Coordinating Centre will acknowledge receipt of the faxed SAE form. Site Investigators should also report SAEs to their provincial adverse event reporting centre as would occur when administering any routine licensed vaccine.

9.2.3 Evaluation and Management

Investigators will follow participants who have developed SAEs during the study until the event has resolved, stabilized, subsided, disappeared, is otherwise explained or the participant is lost to follow-up. Treatment of the SAE is at the sole discretion of the site investigator and according to good medical practice.

10.0 PARTICIPANT RECRUITMENT AND WITHDRAWALS

1. Recruitment

We will recruit and enroll WLWH over a 36-month period starting in January 2023. Recruitment will be at our 10 sites of HIV and/or reproductive care, when WLWH attend for routine care, in collaboration with their healthcare providers. Due to the high frequency of standard clinical HIV care visits, we anticipate that all participants can be recruited during clinic attendance for routine visits.

2. Participant Compliance

In our precursor study of 4vHPV vaccination, 90% of WLWH completed the 3-dose vaccination schedule. As we are recruiting from sites of HIV/reproductive care, these women are generally engaged in care and accustomed to frequent clinical visits that include procedures such as blood draws. Engagement with WLWH confirms their desire to have

their clinical questions answered through appropriate research. Moreover, this vaccine is not publicly funded in all provinces for older women so trial participation provides enhanced access to vaccine.

3. Rate of Loss to Follow Up

In our sample size calculation, we have allowed for 10% loss to follow-up between enrolment and primary outcome (month 7 serology). This is conservative and based on 10% attrition/year in our precursor study.

4. Withdrawals

Investigators or their delegates will attempt to contact those study participants who do not return for study visits. Study personnel will make at least three attempts to contact the participant using various communication means. Each attempt should be documented in the participant source documents.

A participant completing all visits up to and including the Month 24 visit will be considered to have completed the study.

Withdrawals will not be replaced. All withdrawals will be documented including the date of the withdrawal and the reason.

11.0 TRANSPORTATION OF LABORATORY SAMPLES

All shipments of serum samples are to be shipped frozen and prepared by qualified individuals ensuring that all shipments are packed and shipped according to IATA regulations and are to be packed using dry ice.

All shipments of HPV DNA testing aliquots are to be shipped frozen and prepared by qualified individuals ensuring that all shipments are packed and shipped according to IATA regulations.

All samples are to be clearly labeled with participant's 5-digit PID#, date of collection, and visit month.

All shipments must have an accompanying biological shipment listing, with a copy being retained at the site. A biological shipment listing template will be provided to the sites by the Study Coordinating Centre.

Prior to the shipment of any samples, the sites must inform the Study Coordinating Centre regarding the date of shipment to ensure that there is someone at the Coordinating Laboratory to receive the shipment. Confirmation must be received from the Study Coordinating Centre prior to the shipment of any samples. Sites should plan to ship Monday through Wednesday to ensure that samples arrive within 72 hours of packaging to ensure that thawing does not occur before processing.

The Coordinating Centre will arrange for shipment of all samples (serum, vaginal swabs) to the individual laboratories performing the analysis/testing.

12.0 LABORATORY METHODS AND ANALYSES

1. Antibody testing at Merck Laboratories

In order to attain comparability to licensure trial serologic results and comparable studies in immunocompetent persons, antibody assays will be conducted by our collaborator at Merck Laboratories, Q2 Solutions LLC, 2400 Ellis Road, Durham, NC 27703, USA.

Each serum sample will be divided into 2 aliquots: #1 will go to the Merck laboratory for in-house serotesting and #2 will go to the BC Women's Research Lab (Women's Health Research Institute) for storage. Serum anti-HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 immunoglobulin levels will be measured using competitive Luminex immunoassay (cLIA), and reported in arbitrary units (milli-Merck Units per ml [mMU/ml]) relative to the standard curves generated for each HPV type. Antibody titers are determined in a competitive format where type-specific labeled neutralizing antibodies for each type compete with patient serum antibodies for binding to conformation-sensitive neutralizing epitopes on virus like particles. Seropositivity is defined as > 50 mMU/ml for HPV6, 29 mMU/ml for HPV11, 41 mMU/ml for HPV16, 59 mMU/ml for HPV18, 29 mMU/ml for HPV31, 22 mMU/ml for HPV33, 15 mMU/ml for HPV45, 20 mMU/ml for HPV52, and 15 mMU/ml for HPV58.[36]

2. HPV DNA Testing using Self-Collected Vaginal Swabs

All DNA testing for HPV will use vaginal swabs in STM vials. Swabs will be tested by Dr Alberto Severini at the National Microbiology Laboratory, 1015 Arlington Street, Winnipeg, MB R3E 3M4, using a commercially available research assay for the detection of high and low risk HPV genotypes.

We are utilizing a research HPV DNA assay not a clinical HPV assay, and we won't have the test results back in a timely manner as these will be run in batches, maybe 12-24 months after collection, possibly even more. The sensitivity and specificity of this test is not adequate for actionable results. The importance of participating in available clinical screening will be reinforced with participants during the course of study participation.

In cases where the same high risk HPV DNA type is found on 2 occasions, a minimum of 6 months apart, primary care providers will be notified and recommended to follow up with pap or HPV testing, or colposcopy.

3. Use of Retention Self-Collected Vaginal Swabs

The primary purpose of the second swabs, which are collected at 5 of the study visits, is as a retention swab. This swab will be used in the event that the primary swab has inadequate sample or is otherwise compromised. If these swabs are not needed for this purpose, we may test these samples for bacteria that are commonly found in the vagina, and the vaginal samples and blood for a series of viruses that are very common in humans and can be in the body for a long time with no symptoms if the immune system is healthy. We will test for herpes simplex virus or HSV, mononucleosis as well as cytomegalovirus. This testing may include antibody testing and viral DNA and viral RNA testing.

13.0 STATISTICAL ANALYSIS

1. Statistical Analysis Plan

All primary analyses will be performed based on modified intention to treat (mITT). Data missing more than 5% will be imputed using multiple imputation by chained equations to avoid bias.[44] All variables that will be included in analytic models, including all outcome and HPV related variables, with the addition of important demographic variables will be included in imputation equations as advised in the literature.[45]

2. Demographics

Characteristics of the full study population will be described using counts and proportions for categorical variables, means and standard deviations for normally distributed continuous variables, and medians and interquartile ranges for skewed continuous variables. Sex is integral to this project as eligible people must have a cervix, which is biologically only present when female at birth, as we aim to inform the use of the 9vHPV vaccine in individuals with uterine cervices. Gender is also very relevant given that non-binary females and trans men may be included. We will capture self-identified gender through our demographics questionnaire, and examine differences by gender.

3. Primary Analysis

To determine if 2 doses of 9vHPV vaccine are non-inferior to 3 doses in WLWH, we will evaluate serologic response by comparing peak anti-HPV16/18 GMTs individually with 95% CI at 7 months in both groups using linear regression, adjusted for HIV viral load, CD4+ T cell count, and age.[46] We will similarly compare seroconversion rates in the two groups using logistic regression. Adjusting for age and HIV clinical parameters instead of stratifying by them (they are also unlikely to be importantly imbalanced in a trial this size) can improve sensitivity/power.[46] Using immunobridging,[47,48] we will also compare the rate of seroconversion and peak anti-HPV GMTs to previously published two-dose 4vHPV responses in girls and women without HIV [23] and previously published three-dose 9vHPV responses in girls and women without HIV using logistic regression for seroconversion rates and one-sample t-tests for GMT comparisons.[18,49] Immunobridging is a highly accepted method of evaluating HPV vaccines in different groups when a correlate of protection is unknown and efficacy endpoints such as cervical dysplasia take many years to develop. Level of antibody response after two doses will be described by clinical and demographic variables (age, CD4 count, HIV viral load, HPV DNA or antibody positivity at baseline, and lifetime number of sexual partners) using general linear models.

4. Secondary Analyses

1. To compare differences in antibody persistence, longitudinal GMTs will be compared between the two groups (routine vs. extended dosing interval) to determine if there are differences in the rates of antibody persistence at month 24. We will use mixed-effects linear regression on the log-transformed titers to estimate the rate of decline of antibody titers by time since first vaccine dose. Differences in rates will be compared directly using an interaction term between group and time.

2. To evaluate HPV self-sampling acceptability, quantitative survey results will be summarized as frequencies. Comparisons among subgroups (e.g. by age, region, cultural background, and gender) will be conducted using linear regressions.

5. Exploratory Analyses

1. To determine if 2 doses of 9vHPV vaccine are non-inferior to 3 doses in WLWH for the additional 9vHPV types not in the primary outcome, we will evaluate serologic response by comparing peak anti- HPV6/11/31/33/45/52/58 GMTs individually and seroconversion rates with 95% CI at 7 months in both groups using linear and logistic regression, respectively, adjusted for HIV viral load, CD4+ T cell count, and age.

2. As the world is moving towards one-dose HPV vaccine schedules, we will take the opportunity to collect preliminary data on the peak one-dose antibody response at month 1. These data will inform the sample size calculation for a future one-dose trial, as appropriate, and will be reported as anti-HPV16/18 GMTs with 95% CI.

3. To evaluate significant adverse events, the proportion (and 95%CI) of participants who experience significant adverse events will be calculated for the entire study population, and also by group. The types and severities of adverse events will be described.

4. To address vaccine efficacy, we will calculate incidence rates of abnormal cervical cytology and histology (HSIL), and breakthrough persistent HPV infection. HSIL will be described with Kaplan-Meier curves. If sufficient numbers of each are observed, Kaplan-Meier curves will be calculated by age range (21-30, 31-39, 40-55, >55), CD4 count (<200, 200-500, >500), HIV viral load (detectable vs. undetectable), and prior HPV status. Persistent HPV will be described by type of HPV, high vs. low-risk, and vaccine type or not, using Kaplan-Meier curves for HPV acquisition and frequencies and percentage for persistent infections. Given the capability to intervene with early pre-cancerous changes in the cervix, we cannot ethically use cervical cancer as an end point but other efficacy endpoints are critical for an HPV vaccine study as an immune correlate of protection is unknown.

5. To assess the uptake of HPV vaccination of WLWH, a screening log will be kept by each study site to track how many WLWH aged 18-45 were not eligible to participate in the study due to having already received an HPV vaccine. The proportion of women who were previously vaccinated will be calculated for the population of women aged 18-45 at each site and across the country.

6. Planned Subgroup Analyses

Subgroup analyses by gender (woman, gender-diverse) will be conducted if sample size allows, examining differences in all outcomes by gender. Primary and secondary analyses will be analyzed by clinical and demographic variables including: age, ethnicity, region, CD4+ T cell count, HIV viral load suppression (vs. unsuppressed), and HPV DNA or anti-HPV antibody positivity at baseline.

7. Sample Size Calculations

The sample size was calculated based on the primary evaluation of non-inferiority of the immunologic response to 2 vs. 3 doses of 9vHPV vaccine. For ethical reasons, all 2 dose recipients will eventually receive a third dose but we used a dose ranging study design to achieve this end. Using a one-sided alpha = 0.025, a non-inferiority margin of 0.5 based on benchmarks set by Merck for other immunobridging studies leading to licensure,[43] a standard deviation of 1.379 calculated from HPV16 GMTs in our prior cohort of WLWH, and 80% power, we would require 205 participants per group (total: 410). Given an anticipated dose completion rate of 90% based on our prior experience, we aim to recruit 225 participants per group to achieve power to detect non-inferiority in peak 2 vs. 3 dose GMT.

At 6 of our 10 sites, there are >900 WLWH who are unvaccinated and eligible for this study, suggesting there are likely ~1800 eligible women at all sites. We therefore anticipate being able to achieve the target sample size of 450 given that 90% of eligible WLWH screened in our precursor study were enrolled.

14.0 DATA MANAGEMENT

The data safety and monitoring committee (DSMC) will be coordinated through established processes by the CTN and will function at pre-specified intervals to monitor the conduct and progress of the trial, evaluate the accumulating study data including all serious adverse events, recommend protocol changes, alert trial leaders to emerging procedural or ethical issues, and monitor enrolment to ensure timely conduct of the trial. All up to date adverse events will be reported to the DSMC at each meeting to ensure participant safety. All other data including immunogenicity, efficacy, and self-sampling acceptability will be reported to the DSMC as it becomes available throughout the study for assessment of study conduct and progress. Reports from the data management process will be provided to the DSMC to ensure data quality.

Source document data will be transferred to a case report form by study personnel at the investigative sites. The participant identification number (PID) will be assigned to each participant and used to label the case report form and all study samples. Data will be entered through a direct-entry process and managed on Research Electronic Data Capture (REDCap) software.

Data will be entered into a relational database with pre-programmed quality assurance checks. Queries will be resolved with the site study coordinator, with appropriate documentation. Backup copies of the database will be made daily and stored securely at a second location. No personal identifiers will be included in the database. Analysis will be conducted using statistical software (e.g. SAS, SPSS, or R).

All personal information pertaining to participants will be securely stored at sites in a locked room, under the supervision of the site study coordinator(s) and accessible to study staff only. Where

electronic databases are used as mechanisms for participant tracking etc. these databases will be password protected and available only to specified study staff and site investigators.

15.0 ADMINISTRATIVE MATTERS

1. Protocol Amendment Procedure

No modification of this protocol will be allowed unless discussed and approved with the Study Coordinating Centre and a filed and approved change to the protocol is made with local REBs, when appropriate.

Documentation of the amendments and REB certification will be maintained at each investigative site and are required prior to implementation.

The Study Coordinating Centre reserves the right to suspend or terminate the clinical trial at any or all participating centres for any reason including but not limited to: safety, ethical issues or severe non-compliance. All investigative sites will be consulted and notified in this instance. REB notification is required.

2. Records Retention

Data and study documents (all sites) will be stored securely for 15 years, after which they will be destroyed in keeping with privacy and confidentiality regulations and guidelines.

All personal health information pertaining to participants will be securely stored in a locked area, under the supervision of the site study coordinator(s) and accessible to study staff only. The location of storage of the study files must be documented and revised if the location changes. The Study Coordinating Centre must be aware of the storage location at each site and changes to the location must be provided in writing.

3. Clinical Study Report

Interim study progress reports, as well as the final report, will be submitted to the Canadian Institutes of Health Research.

4. Knowledge Translation

Manuscripts of the study findings will be prepared for submission to peer reviewed publications. Study findings will also be presented at appropriate scientific meetings. Study results will be disseminated to the community at two community events. One will take place following the primary endpoint (Month 7) and another following the end of the study (Month 24). Results will also be available on clinicaltrials.gov.

16.0 REFERENCE LIST

1. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. The Lancet Global Health. 2020;8(2):e191-e203.
2. Canadian Partnership Against Cancer. Canada acts to meet WHO Call to eliminate cervical cancer. 2020 [cited; Available from: https://www.partnershipagainstcancer.ca/news-events/news/article/eliminate-cervical-cancer/
3. Government of Canada. Cervical Cancer. 2017 [cited February 2020]; Available from: https://www.canada.ca/en/public-health/services/chronic-diseases/cancer/cervical-cancer.html
4. Young TK, Kliewer E, Blanchard J, Mayer T. Monitoring disease burden and preventive behavior with data linkage: cervical cancer among aboriginal people in Manitoba, Canada. American Journal of Public Health. 2000;90(9):1466-8.
5. Ferenczy A, Coutlee F, Franco E, Hankins C. Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: a review of recent developments. Canadian Medical Association Journal. 2003;169(5):431-4.
6. UNAIDS. Global HIV & AIDS statistics — 2019 fact sheet. 2019 [cited February 2020]; Available from: https://www.unaids.org/en/resources/fact-sheet
7. Public Health Agency of Canada. Summary: Estimates of HIV Incidence, Prevalence and Canada's Progress on Meeting the 90-90-90 HIV Targets, 2016. Ottawa; 2018.
8. Brickman C, Palefsky JM. Human Papillomavirus in the HIV-Infected Host: Epidemiology and Pathogenesis in the Antiretroviral Era. Current HIV/AIDS Reports. 2015;12(1):6-15.
9. Dolev JC, Maurer T, Springer G, Glesby MJ, Minkoff H, Connell C, et al. Incidence and risk factors for verrucae in women. AIDS (London, England). 2008;22(10):1213-9.
10. Massad LS, Xie X, Burk R, Keller MJ, Minkoff H, D'Souza G, et al. Long-term cumulative detection of human papillomavirus among HIV seropositive women. AIDS (London, England). 2014;28(17):2601-8.
11. Abraham AG, D'Souza G, Jing YZ, Gange SJ, Sterling TR, Silverberg MJ, et al. Invasive Cervical Cancer Risk Among HIV-Infected Women: A North American Multicohort Collaboration Prospective Study. JAIDS. 2013;62(4):405-13.
12. Parham GP, Sahasrabuddhe VV, Mwanahamuntu MH, Shepherd BE, Hicks ML, Stringer EM, et al. Prevalence and predictors of squamous intraepithelial lesions of the cervix in HIV-infected women in Lusaka, Zambia. Gynecologic Oncology. 2006;103(3):1017-22.
13. Villa A, Patton LL, Giuliano AR, Estrich CG, Pahlke SC, O'Brien KK, et al. Summary of the evidence on the safety, efficacy, and effectiveness of human papillomavirus vaccines: Umbrella review of systematic reviews. The Journal of the American Dental Association (1939). 2020;151(4):245-54.e24.
14. Gakidou E, Nordhagen S, Obermeyer Z. Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities. PLoS medicine. 2008;5(6):e132-e.
15. Zizza A, Banchelli F, Guido M, Marotta C, Di Gennaro F, Mazzucco W, et al. Efficacy and safety of human papillomavirus vaccination in HIV-infected patients: a systematic review and meta-analysis. Scientific reports. 2021;11(1):4954-13.
16. Whitworth HS, Gallagher KE, Howard N, Mounier-Jack S, Mbwanji G, Kreimer AR, et al. Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no

vaccination or standard three and two-dose vaccination regimens: A systematic review of evidence from clinical trials. Vaccine. 2020;38(6):1302-14.
17. Immunisation TJCoVa. JCVI interim advice on a one-dose schedule for the routine HPV immunisation programme; 2022.
18. Money DM, Moses E, Blitz S, Vandriel SM, Lipsky N, Walmsley SL, et al. HIV viral suppression results in higher antibody responses in HIV-positive women vaccinated with the quadrivalent human papillomavirus vaccine. Vaccine. 2016;34(40):4799-806.
19. Kahn JA, Xu J, Kapogiannis BG, Rudy B, Gonin R, Liu N, et al. Immunogenicity and safety of the human papillomavirus 6, 11, 16, 18 vaccine in HIV-infected young women. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2013;57(5):735-44.
20. Kojic EM, Kang M, Cespedes MS, Umbleja T, Godfrey C, Allen RT, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;59(1):127-35.
21. Boey L, Curinckx A, Roelants M, Derdelinckx I, Van Wijngaerden E, De Munter P, et al. Immunogenicity And Safety Of The Nine-Valent Human Papillomavirus Vaccine In Solid Organ Transplant Recipients And Hiv-Infected Adults. Clinical infectious diseases. 2020.
22. National Committee on Immunization. Updated Recommendations on Human Papillomavirus (HPV) Vaccines: 9-valent HPV vaccine 2-dose immunization schedule and the use of HPV vaccines in immunocompromised populations; 2017.
23. Dobson SRM, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 Doses of HPV Vaccine in Younger Adolescents vs 3 Doses in Young Women: A Randomized Clinical Trial. JAMA. 2013;309(17):1793-802.
24. European Medicines Agency. Gardasil-H-C-705-WS-472: EPAR - Assessment Report - Variation; 2014 5 June 2014.
25. McClymont E, Lee M, Raboud J, Coutlée F, Walmsley S, Lipsky N, et al. The Efficacy of the Quadrivalent Human Papillomavirus Vaccine in Girls and Women Living With Human Immunodeficiency Virus. Clinical Infectious Diseases. 2019;68(5):788-94.
26. Ogilvie GS, van Niekerk D, Krajden M, Smith LW, Cook D, Gondara L, et al. Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months: The HPV FOCAL Randomized Clinical Trial. JAMA. 2018;320(1):43.
27. Moses E, Pedersen HN, Mitchell SM, Sekikubo M, Mwesigwa D, Singer J, et al. Uptake of community-based, self-collected HPV testing vs. visual inspection with acetic acid for cervical cancer screening in Kampala, Uganda: preliminary results of a randomised controlled trial. Tropical Medicine & International Health. 2015;20(10):1355-67.
28. Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet (London, England). 2020.
29. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet (London, England). 2020.
30. de Pokomandy A, Burchell AN, Salters K, Ding E, O'Brien N, Bakombo DM, et al. Cervical cancer screening among women living with HIV: a cross-sectional study using the baseline questionnaire data from the Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS). CMAJ open. 2019;7(2):E217.

31. UN Women. Facts and figures: HIV and AIDS. 2018 [cited 2020; Available from: https://www.unwomen.org/en/what-we-do/hiv-and-aids/facts-and-figures
32. World Health Organization. Human papillomavirus vaccines: WHO position paper, October 2014. Geneva; 2014.
33. LaMontagne DS, Bloem PJN, Brotherton JML, Gallagher KE, Badiane O, Ndiaye C. Progress in HPV vaccination in low- and lower-middle-income countries. International journal of gynecology and obstetrics. 2017;138:7-14.
34. Sankaranarayanan RD, Prabhu PRM, Pawlita MMD, Gheit TP, Bhatla NMD, Muwonge RP, et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. Lancet Oncology, The. 2016;17(1):67-77.
35. Ferris DG, Samakoses R, Block SL, Lazcano-Ponce E, Restrepo JA, Mehlsen J, et al. 4-Valent Human Papillomavirus (4vHPV) Vaccine in Preadolescents and Adolescents After 10 Years. Pediatrics. 2017;140(6).
36. Roberts C, Green T, Hess E, Matys K, Brown MJ, Haupt RM, et al. Development of a human papillomavirus competitive luminex immunoassay for 9 HPV types. Human Vaccines & Immunotherapeutics. 2014;10(8):2174-103.
37. Eklund C, Forslund O, Wallin K-L, Dillner J. Continuing global improvement in human papillomavirus DNA genotyping services: The 2013 and 2014 HPV LabNet international proficiency studies. Journal of clinical virology. 2018;101:74-85.
38. Sherman ME, Schiffman MH, Lorincz AT, Herrero R, Hutchinson ML, Bratti C, et al. Cervical specimens collected in liquid buffer are suitable for both cytologic screening and ancillary human papillomavirus testing. Cancer. 1997;81(2):89-97.
39. Latsuzbaia A, Tapp J, Nguyen T, Fischer M, Arbyn M, Weyers S, et al. Analytical performance evaluation of Anyplex II HPV28 and Euroarray HPV for genotyping of cervical samples. Diagnostic microbiology and infectious disease. 2016;85(3):318-22.
40. Cornall AM, Poljak M, Garland SM, Phillips S, Machalek DA, Tan JH, et al. HPV genotype-specific concordance between EuroArray HPV, Anyplex II HPV28 and Linear Array HPV Genotyping test in Australian cervical samples. Papillomavirus research. 2017;4:79-84.
41. Kwon M-J, Roh KH, Park H, Woo H-Y. Comparison of the Anyplex II HPV28 assay with the Hybrid Capture 2 assay for the detection of HPV infection. Journal of clinical virology. 2014;59(4):246-9.
42. Oštrbenk A, Xu L, Arbyn M, Poljak M. Clinical and Analytical Evaluation of the Anyplex II HPV HR Detection Assay within the VALGENT-3 Framework. Journal of clinical microbiology. 2018;56(11).
43. Ostrbenk A, Xu L, Arbyn M, Poljak M. Clinical and Analytical Evaluation of the Anyplex II HPV HR Detection Assay within the VALGENT-3 Framework. J Clin Microbiol. 2018 Nov;56(11).
44. van Buuren S, Groothuis-Oudshoorn CGM. mice: Multivariate Imputation by Chained Equations in R. Journal of statistical software. 2011;45(3).
45. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in medicine. 2011;30(4):377-99.
46. Hernández AV, Steyerberg EW, Habbema JDF. Covariate adjustment in randomized controlled trials with dichotomous outcomes increases statistical power and reduces sample size requirements. Journal of clinical epidemiology. 2004;57(5):454-60.

47. Lowy DR, Herrero R, Hildesheim A, Participants in the INCIwoPEfPHPVVT. Primary endpoints for future prophylactic human papillomavirus vaccine trials: towards infection and immunobridging. The Lancet Oncology. 2015;16(5):e226-e33.
48. Van Damme P, Olsson SE, Block S, Castellsague X, Gray GE, Herrera T, et al. Immunogenicity and Safety of a 9-Valent HPV Vaccine. PEDIATRICS. 2015;136(1):E28-E39.
49. Joura EA, Giuliano AR, Iversen O-E, Bouchard C, Mao C, Mehlsen J, et al. A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. The New England Journal of Medicine. 2015;372(8):711-23.
50. McClymont E, Ogilvie G, Albert A, Johnston A, Raboud J, Walmsley S, et al. Impact of quadrivalent HPV vaccine dose spacing on immunologic response in women living with HIV. Vaccine. 2020.