CLINICAL STUDY PROTOCOL

A multicenter, randomized controlled trial of the efficacy, safety and immunogenicity of the 9-valent human papillomavirus (HPV) vaccination in preventing recurrence of high-grade anal dysplasia in HIV-positive men who have sex with men (MSM)

Sub-study of the HPV-SAVE Study: HPV and HPV Vaccine Evaluation in men who have sex with men

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Protocol No. 53205 (CTN 324)
Version #6.0
Sponsor: Dr. Irving Salit

GCP Statement

This clinical study will be conducted in accordance with applicable Health Canada regulations, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on current Good Clinical Practice (GCP), and the Declaration of Helsinki.

Confidentiality Statement

This clinical study protocol contains information which is of a confidential, trade-secret or proprietary nature. The protocol is for the use of [Sponsor or Sponsor-Investigator] and [his/her] designated representatives participating in the investigational trial. It is not to be disclosed to any other person or party without the prior written approval of [Sponsor or Sponsor-Investigator].

INVESTIGATOR AGREEMENT

Protocol Title:	A multicenter, randomized controlled trial of the efficacy, safety and immunogenicity of the 9-valent human papillomavirus (HPV) vaccination in preventing recurrence of high-grade anal dysplasia in HIV-positive men who have sex with men (MSM)
Protocol No.:	53205 (CTN 324)
Version No.:	6.0
Date:	18-Jul-2024

This clinical study will be conducted in accordance with applicable Health Canada regulations, ICH guidelines on current GCP, and the Declaration of Helsinki.

I confirm that I have read and understand this protocol and I agree to conduct this clinical study in accordance with the design and specific provisions of the protocol, with the exception of a change intended to eliminate an immediate hazard to participants. Any deviation from the study protocol will be documented in the case report form.

I agree to promptly report to the applicable ethics boards any changes in the research activity and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without prior ethics and sponsor approval, except where necessary to ensure the safety of study participants.

Name	Signature	Date (dd-mmm-yyyy)

Protocol Summary

Full Title: A multicenter, randomized controlled trial of the efficacy, safety and immunogenicity of the 9-valent human papillomavirus (HPV) vaccination in preventing recurrence of high-grade anal dysplasia in HIV-positive men who have sex with men (MSM)

Short Title: HPV-SAVE Merck Sub-study (CTN 324)

Study Population
Men who have sex with men, aged 18 or older, HIV-positive and on a stable antiretroviral regimen

Study Design
A multi-site, randomized controlled trial

Study Duration
Six years

Study Intervention
9-valent HPV vaccine

Primary Efficacy Objective
1. To determine the role of the 9-valent HPV vaccine in preventing recurrence of high-grade, anal intraepithelial neoplasia (HGAIN) in those treated with ablative therapy (secondary prevention). Recurrence includes HGAIN at the original or at a new site ("metachronous" site).

Secondary Efficacy Objectives
1. To determine the short-term immunogenicity of the 9-valent HPV vaccine in HIV-infected men, four weeks following the third dose of the vaccine.
2. To determine the reduction in anal carriage of vaccine HPV types post-vaccination

Primary Safety Objective
1. To determine the frequency of vaccine-related adverse events.

Hypotheses
1. In those individuals vaccinated with the 9-valent HPV vaccine and receiving ablative therapy for high-grade anal dysplasia, the recurrence rate for dysplasia will be reduced by 50% within the 36 months of follow-up.
2. The 9-valent HPV vaccine will be highly immunogenic in vaccinated HIV-positive individuals.
3. The 9-valent vaccine will be safe in HIV-positive individuals.
4. The 9-valent vaccine will reduce anal carriage of vaccine HPV types.

ABBREVIATIONS AND DEFINITONS

Acronym / Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
AIN	Anal intraepithelial neoplasia
cART	Combination antiretroviral therapy
CATIE	Community AIDS Treatment Information Exchange
CD4/CD8	Cluster of differentiation 4/8
CDC	Centres for Disease Control and Prevention
CIHR	Canadian Institutes of Health Research
CI	Confidence intervals
CRF	Case report form
CROI	Conference on Retroviruses and Opportunistic Infections
DAIDS-AE	Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
DSMB	Data Safety and Monitoring Board
DNA	Deoxynucleic acid
EC	Electrocautery
ELISA	Enzyme-linked immunosorbent assay
GEE	Generalized estimating equation
GMT	Gemoetric mean titres
HGAIN	High-grade anal intraepithelial neoplasia (also designated AIN2 or AIN3)
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HPV-SAVE	The 'HPV Screening and Vaccine Evaluation' Study team
HRA	High-resolution anoscopy
HR-HPV	High-risk (oncogenic) human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
ITT	Intention-to-treat
IRC	Infrared coagulation

MSM	Men who have sex with men
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
NACI	National Advisory Committee on Immunizations
Papanicolaou	A method to test for potentially pre-cancerous and cancerous changes
PCR	Polymerase chain reaction
SCC	Squamous cell carcinoma
RNA	Ribonucleic acid
SAE	Serious Adverse Event
STI	Sexually transmitted infection

1.0 General Information

1.1 Briefer on the HPV-SAVE Team

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) worldwide. Infection by certain high-risk oncogenic types of HPV (HR-HPV) is the major cause of several cancers in men, notably squamous cell carcinoma (SCC) of the anal canal. Rates of anal infection with these HR-HPV strains, and the resultant high-grade anal dysplasia and anal cancer are much higher in men who have sex with men (MSM) than in the general population. Co-infection with human immunodeficiency virus (HIV) further amplifies this burden, making the rates of anal SCC in HIV-positive MSM higher than the historic rates of cervical cancer prior to the adoption of routine cervical cytology screening. Despite these alarming statistics, there are no established protocols for optimal screening and treatment of anal HPV and cancer precursors, nor has there been any widespread rollout of organized screening programs anywhere in Canada. Further, not only does HPV directly cause significant disease in these men, but there is growing epidemiologic evidence that HPV infection may enhance sexual transmission of HIV. These significant knowledge gaps translate into fundamental deficiencies in care for HIV-positive MSM.

The HPV Screening and Vaccine Evaluation in MSM (HPV-SAVE) study team was funded by the Canadian Institutes of Health Research (CIHR) via its Boys' and Men's Health Team Grant Competition. It recruited a large group of MSM from various Ontario and Vancouver clinics, in order to carry out a number of different studies. The HPV-SAVE team brought together community and internationally recognized experts in HPV and HIV disease and mucosal immunology, to better define the optimal approaches for primary and secondary prevention and treatment of HPV-associated anal disease among HIV-positive MSM, and to explore biological mechanistic evidence regarding the potential role of HPV as a co-factor for HIV transmission. This will yield critical information which can lead to improvement in the health of MSM, and will provide a foundation on which to build large-scale screening and treatment trials on a national level. A key part of this research program

involves an analysis of the potential role played by the HPV vaccine in the overall management of HIV-positive MSM.
Planned vaccine-related projects include:

- A mixed-methods analysis of the knowledge, attitudes, and acceptability of HPV vaccination amongst HIV-positive MSM, through quantitative (e.g. cross-sectional survey) and qualitative (e.g. in-depth interviews) means.
- A comprehensive assessment of the 9-valent HPV vaccine in HIV-positive MSM, including safety and immunogenicity, as well as its potential role in secondary prevention of high-grade anal dysplasia. This is the study on which the current proposal is based.

2.0 Background Information

2.1 Background

Advances in the treatment of HIV-infected individuals with the advent of the combination antiretroviral therapy (cART) era has led to dramatic reductions in mortality and morbidity [1,2]. These dramatic strides in survival within HIV-positive populations have led to a focus on longer-term morbidities in these individuals, including malignancies. Indeed, an increase in a variety of malignancies in HIV-infected individuals has been noted in the cART era [3-5]. Amongst these are cancers associated with HPV, responsible for the vast majority of cervical cancers (itself a well-established acquired immune deficiency syndrome (AIDS)-defining illness), and 40-90% of anal, vulvar, vaginal, penile, and oropharyngeal cancers [6]. More specifically, a recent meta-analysis indicates that the overall prevalence of HPV in anal carcinoma is approximately 84%, with HPV type 16 being isolated in 73% of all cases, making it the most prevalent type implicated in anal carcinoma [7].

Though infrequent at a rate of one per 100,000, squamous cell anal carcinoma is on the rise in the general population [8]. It occurs at significantly higher rates in HIV-positive men – particularly among MSM – with an estimated rate of 60 to 160 per 100,000 [9-12]. A recent study of thirteen North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) with over 34,000 HIV-infected patients, found that anal cancer rates were highest in HIV-infected MSM, with a rate of 131 per 100,000 person years [13]. In fact, rates of anal cancer among HIV-infected MSM are comparable to rates of cervical cancer in women prior to the adoption of routine screening for cervical dysplasia [14]. In addition to its etiologic association with HPV, anal cancer shares many similarities with cervical cancer. Both are squamous cell cancers occurring at the squamo-columnar junction [15,16], and both likely arise from histologically similar, dysplastic precursor lesions [17,18]. It is postulated that a critical step in anal cancer carcinogenesis is the establishment of persistent infection (conventionally defined as greater than six or twelve months) with oncogenic HPV in the anal canal [18,19]. Though the majority of HPV infections are considered transient and will eventually clear even in HIV-positive individuals [20], HIV-positive individuals have higher rates of persistent infection, especially with oncogenic HPV types [21,22].

Of the greater than 170 HPV types, over 30 favour the anogenital area, and on the basis of epidemiologic and phylogenetic data, these have been classified by the International Agency for Research on Cancer (IARC) as outlined in Table 1 [23]:

Table 1: Classification of HPV by IARC Monograph Working Group

Group	HPV Types	Comments
Alpha HPV Types		
1	16	Most potent type; cancer caused at several sites
1	18,31,33,35,39,45,51,52,56, 58, 59	Sufficient evidence for cervical cancer
2A	68	Limited human evidence; strong mechanistic evidence for cervical cancer
2B	26,53,66,67,70,73,82	Limited evidence in humans for cervical cancer
2B	30,34,69,85,97	Classified by phylogenetic analogy to HPV types with sufficient or limited evidence in humans.
3	6,11	"
Beta HPV Types		
2B	5 and 8	Limited evidence for skin cancer
3	Other beta/gamma types	"

The vast majority of anal cancers (as well as cervical cancers) are caused by two high-risk HPV types: HPV type 16 and HPV type 18, felt to be responsible for 66% and 5% of anal cancers, respectively [24]. However, a recent study from France examining the distribution of HPV types in cases of anal cancer found even more dramatic results: HPV was found in 96.7% of all cases, with HPV-16 being the most prevalent type (75%), with other high-risk types (HPV-18, -52, -33, and -51) found in 4% to 6% of cases [25]. Further, HPV-16 and -18 – either alone or in combination – were found in over 78% of cases. HPV lesions caused by low-risk types include condylomata (commonly known as 'genital warts'), of which 90% are caused by HPV types 6 and 11 [26].

Prevention strategies for anal cancers have emerged that are analogous to strategies used in cervical cancer screening. They rely on a combination of cytology (Papanicolaou, or Pap smear) and high-resolution anoscopy (HRA; analogous to colposcopy), both of which screen for high-grade anal intraepithelial neoplasia (HGAIN; typically graded as anal intraepithelial neoplasia (AIN) AIN-2 or -3) [18,27]. Despite the clear evidence indicating the benefit (in cancer reduction) of screening and treatment procedures in cervical cancer screening, no large rigorous studies have been published to assess the performance of such strategies in anal cancer screening in either men or women. The ANCHOR study is a US study comparing treatment of anal pre-cancerous lesions (mostly with EC), to observation alone; it was prematurely stopped by the study's Data Safety Monitoring Committee, and the results are now published. In brief, in the more than 4,000 participants enrolled with a median follow-up of 26 months, participants in the treatment arm were 57% less likely to progress to cancer (95% confidence interval, 6 to 80; p=0.03). Though the ANCHOR study examined treatment of precancers and not cancer screening per se, the findings from this study lend clear evidence-based support for anal cancer screening and its goal of identifying precancers [(43)].

In addition to the scant literature on the efficacy of screening programs for anal cancer and HPV in all men – but particularly those who are HIV-positive – there remains an even

greater paucity of data on issues surrounding primary prevention of HPV. The HPV quadrivalent recombinant vaccine, or Gardasil®, protects against HPV types 6 and 11, which are the most common types implicated in condylomata acuminata (anogenital warts), as well as the most common oncogenic strains, types 16 and 18 [24,26]. The use of this vaccine has been shown to prevent persistent cervical HPV infection caused by vaccine types in women, as well as preventing nearly all high-grade genital lesions in women – the latter of which are considered precursor lesions to invasive cancers [28-30]. Additionally, a retrospective pooled analysis of two large efficacy trials of quadrivalent HPV vaccine has also demonstrated a treatment effect from HPV vaccine in preventing recurrences of previously treated high grade cervical disease [31].

Few studies have been done on the use of the quadrivalent HPV vaccine in men; there has only been one study examining the use of the HPV vaccine in HIV-positive men, and this study found the vaccine to be safe and immunogenic [32]. Overall, these studies have shown promise in demonstrating a reduction in vaccine-type genital lesions in young men who were vaccinated versus those receiving placebo [33], evidence of protection against HGAIN in MSM [34], and a 50% reduction rate in HGAIN recurrence in MSM previously treated for dysplastic lesions [35]. This latter study lays the foundation of the currently proposed study. However, the role of the HPV vaccine in secondary prevention of HGAIN has not previously been examined in a systematic, prospective way. Given the unacceptably high rates of HGAIN recurrence in those having undergone ablative therapy (from 62% to 91% within two years, with rates almost two-fold higher in HIV-positive MSM) [36], **exploring this potentially novel benefit of the HPV vaccine is certainly warranted and could potentially change the way clinicians address HPV-related disease in this high-risk group**.

Until recently, there existed no standard recommendation for the use of HPV vaccinations in males, regardless of HIV serostatus; however, these studies have prompted the Centres for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) to recommend that boys be routinely vaccinated for HPV beginning at age 11 or 12 [37]. Canada's National Advisory Committee on Immunizations (NACI) went further, recommending vaccination of all males between 9 and 26 years of age, as well as in any MSM 9 years of age or older.

Gardasil-9 is a novel, 9-valent HPV recombinant vaccine, which expands the coverage of oncogenic HPV types, with the addition of HPV types 31, 33, 45, 52, and 58 to the existing quadrivalent vaccine types. The addition of these five oncogenic types is estimated to improve cancer coverage to 90% (versus 70% for the quadrivalent vaccine) [38]. With its expanded coverage of oncogenic HPV types, its proven efficacy in primary prevention and its potential role in mitigating HGAIN recurrences – all coupled with the disproportionate burden of HPV-related anal cancers borne by HIV-positive MSM – it is critical that its use be comprehensively assessed in this very high-risk population.

2.2. Rationale for the study

This study will attempt to address some of the limitations in the current literature on HPV vaccinations in the following ways. First, the objective of examining the potential

secondary prevention role of this vaccine in preventing HGAIN has never been examined in a prospective manner. Second, the safety and immunogenicity objectives relating to the 9-valent HPV vaccine will add to the growing research as it includes HIV-positive men – a population not yet considered in studies of this novel vaccine. Third, in contrast to the previously cited safety and immunogenicity study in HIV-positive men, there are no exclusions based on severity of HIV disease, level of immunosuppression or age. The latter is particularly relevant since there are data indicating that men may remain at high risk for contracting HPV throughout their lives [39]. Fourth, we need more information on the effect of the HPV vaccine on possible reduction on anal HPV carriage, especially since chronic HPV carriage is associated with anal cancer. The current literature on HPV vaccination in men has tended to be either quite focused or exclusionary, resulting in data that is not generalizable. Thus, there is much knowledge to be gained from a study such as this, which takes a comprehensive approach in including HIV-positive men of varied age and at various points in their disease.

3.0 Study Objectives and Hypotheses

3.1 Study Objectives

3.1.1 Primary efficacy objective

1. To determine the role of the 9-valent HPV vaccine in preventing recurrence of HGAIN in those treated with Electrocautery ablative therapy (secondary prevention). Recurrence includes HGAIN at the original or at a new site (”metachronous” site).

3.1.2 Secondary efficacy objectives

1. To determine the short-term immunogenicity of the 9-valent HPV vaccine in HIV-infected men, four weeks following the third dose of the vaccine.
2. To determine if there was a reduction in anal carriage of vaccine HPV types.

3.1.3 Primary safety objective

1. To determine the frequency of vaccine-related adverse events.

3.2 Study Hypotheses

1. In those individuals vaccinated with the 9-valent HPV vaccine receiving ablative therapy for high-grade anal dysplasia, the recurrence rate for dysplasia will be reduced by 50% within the 36 months of follow-up.
2. The 9-valent HPV vaccine will be highly immunogenic in vaccinated HIV-positive individuals.
3. The 9-valent vaccine will be safe in HIV-positive individuals.
4. The 9-valent vaccine will reduce anal carriage of vaccine HPV types.

4.0 Study Design

4.1 Description

This will be a randomized, open-label multicentre clinical trial consisting of two arms (immediate versus delayed vaccination) assessing the efficacy, safety and immunogenicity of the 9-valent recombinant HPV vaccine in HIV-positive males 18 years of age and older.

The delayed arm will receive Gardasil-9 12 months after the immediate arm. Similarly, appropriate follow-ups and testing in the delayed arm will occur 12 months after the immediate arm.

Participants for the proposed study will be recruited from Canadian primary care and anoscopy centres in Toronto and Vancouver who were involved in projects making up our HPV-SAVE team grant. Other sites will possibly be added as the study progresses.

4.2 Study Outcomes

Primary efficacy outcome (Secondary prevention): The primary outcome will be the proportion of participants in each arm with at least one recurrence of biopsy-proven HGAIN (AIN-2/3) during 36 months following initially successful treatment of HGAIN.

"Successful treatment" refers to a biopsy-proven HGAIN lesion treated with ablative therapy (electrocautery (EC)) with repeat biopsy of the same lesion 2-3 months thereafter demonstrating no further evidence of HGAIN (meaning that the follow-up biopsy is either AIN-1 or normal). For the purposes of this study, re-development of HGAIN at the site of the "successful treatment" as well as metachronous HGAIN lesions (HGAIN lesions at a new site) will be recorded as a recurrence.

Secondary efficacy outcome (Immunogenicity): 1. The geometric mean titres (GMT) of antibody to each vaccine type above a pre-specified, validated cut-off. For this measure, immunogenicity will be measured as the proportion of participants with GMT of antibody to each vaccine type above a pre-specified, validated cut-off, using a Luminex-based immunoassay [40-42]. Currently, these values for the HPV types present in the 9-valent vaccine are: HPV-6, 30 milli-Merck units/ml (mMU/mL); HPV-11, 16 mMU/mL; HPV-16, 20 mMU/mL; HPV-18, 24 mMU/mL; HPV-31, 10 mMU/mL; HPV-33, 8 mMU/mL; HPV-45, 8 mMU/mL; HPV-52, 8 mMU/mL; and HPV-58, 8 mMU/mL [42].

2. Reduction in anal carriage of vaccine HPV types. Repeated detection of anal HPV (Table 2) will indicate the duration of carriage. This will be compared between the early and delayed vaccine groups.

Primary safety outcome: The frequency of vaccine-related adverse events, using standardized measures as done in previous HPV vaccine trials.

5.0 Selection of Participants

5.1 Number of Participants

A combined total of 228 HIV-positive male participants will be enrolled in the study at two research sites in Canada.

5.2 Participant Inclusion Criteria

1. Males, aged ≥ 18 years at Screening;
2. Physician or laboratory documentation of HIV-1 infection (enzyme-linked immunosorbent assay [ELISA] and Western Blot);

3. AIN-2 or -3 (HGAIN) found on biopsy of anal canal lesion(s), and willingness of the participant to undergo ablative therapy which is standard of care in most screening clinics; These HGAIN participants will be those who are already followed in our anal cancer screening clinics or they may new, routine referrals from primary care;
4. History of any sexual activity with men, or both men and women, where sexual activity is defined as oral, vaginal, or anal intercourse;
5. For those on cART, the participant must be on a stable regimen (i.e. virologically suppressed with HIV-1 ribonucleic acid (RNA) below the assay's limit of detection for minimum six months). This will minimize confounding from dramatic shifts in viral load and/or CD4+ T lymphocyte (CD4) count;
6. For those individuals that are not on cART, there must be no immediate plans to initiate cART in the next six months. There will be no lower limit cut-off for CD4 count;
7. An ability to give informed consent;
8. An ability to attend clinic for all study visits.

5.3 Participant Exclusion Criteria

1. Known hypersensitivity to any component of the HPV vaccine (e.g. *Saccharomyces cerevisiae* yeast, Amorphous Aluminium Hydroxyphosphate Sulfate adjuvant);
2. Current history of cancer of the anogenital regions (e.g. penile, anal, or rectal) or of the oropharyngeal area (e.g. oral cavity, upper airway);
3. Previous HPV immunization.

5.4 Recruitment of Participants

Multiple strategies will be employed to achieve adequate and timely participant enrolment, while achieving the target sample size. The HPV-SAVE team grant comprised a number of different research projects with participants from over a dozen primary care HIV and specialty HIV clinics in Toronto, and Vancouver. Participants in this vaccine study will be invited to have anal cancer screening; many will be from this same pool of individuals in HPV-SAVE. Those meeting the inclusion criteria (e.g. diagnosed with HGAIN either at screening or previously as part of another screening program such as HPV-SAVE) will be invited to participate. Eligible patients at all study sites will also be approached for enrolment in this current study.

Detailed materials about the trial will be provided to potential sub-study participants during the informed consent process. A log will be maintained of all individuals who refuse participation, along with accompanying demographic (age, sex, ethnicity) and relevant clinical (CD4 count, viral load, cART regimen, HIV exposure category) characteristics to allow for a comparison between participants and non-participants.

5.5 Withdrawal of Participants

Participants are free to withdraw from the study at any time and for whatever reason, specified or unspecified, and without prejudice to his or her medical care by a physician. A participant may be withdrawn from the study due to the reasons listed below including, but not limited to:

- Participant's request.
- Site Investigator's request.
- Sponsor-Investigator's request.
- Safety reasons (e.g. Serious adverse event, potential significant drug interaction).
- Participant non-compliance with study procedures.
- Participant's use of, or need for, concomitant therapy liable to interfere with the interpretation of study endpoints. Investigators will report all such information on the applicable electronic Case Report Form (eCRF) and decide whether the participant is to be withdrawn.
- Loss to follow-up. An Investigator or delegate will attempt to reach a participant by phone, email, and/or text at least 3 times during a 30-day period before considering the participant lost-to-follow-up. These actions will be reported on the appropriate source documents in the participant's file.

Participants that are withdrawn before the full course of 3 vaccinations will be replaced to ensure a minimum of **103** participants complete the study in both arms.

5.4 Study Flowchart

Study Visits	Screening * (-3 months) Screening	Baseline * Day 0 Visit 1	Mo. 2 (+/- 2 weeks) Visit 2	Mo. 6 (+/- 2 weeks) Visit 3	Mo.7 (+/- 3 days) Visit 4	Mo. 12 (+/- 2 weeks) Visit 5	Mo.14 (+/- 2 weeks) Visit 6	Mo. 18 (+/- 2 weeks) Visit 7	Mo.19 (+/- 3 days) Visit 8	Mo. 24 (+/- 2 weeks) Visit 9	Mo. 30 (+/- 2 weeks) Visit 10	Mo. 36 ^ (+/- 1 month) Visit 11	Mo. 48 (+/- 1 month) Visit 12
Informed consent	X												
Full health history, Patient Intake Questionnaire & physical exam	X												
Focused health history, Clinical Questionnaire & targeted physical exam #		X		X		X		X		X	X	X	D
High-resolution anoscopy, anal cytology (Pap) & biopsies #	X	X		X		X		X		X	X	X	D
Vaccination – Immediate arm		I	I	I									
Vaccination – Delayed arm						D	D	D					
Vaccine diaries – Immediate vaccine arm		I	I	I									
Vaccine diaries– Delayed vaccine arm						D	D	D					
Adverse events monitoring	X	X	I	X	I	X	D	X	D	X	X	X	D
Ablative treatment for dysplasia #	X	X		X		X		X		X	X	X	D
Anal swab for HPV DNA/ genotyping		I			I	D			D	I		X	D
HPV antibody testing (GMT)		I			I	X			D	X		X	D
Randomization (1:1)		X											

* Screening and Baseline visits may be combined for participants who have been diagnosed with HGAIN within a timeframe as assessed by the site investigator, in which case HRA will be done only once.

Targeted physical examination, Biopsies and Ablative treatment for dysplasia will be done on an 'as needed' basis, when clinically indicated.

X = Assessments for ALL participants
I = Assessments for IMMEDIATE Arm only
D = Assessments for DELAYED Arm only

Mo. 2 and Mo 7 Visits – for IMMEDIATE Arm only
Mo. 2 must be at least 30 days from Baseline visit date for IMMEDIATE arm
Mo. 7 visit must be at least 30 days from Mo. 6 visit date

Mo. 14, Mo. 19, and Mo. 48 Visits – for DELAYED Arm only
Mo. 14 must be at least 30 days from Mo. 12 visit date for DELAYED arm
Mo. 19 visit must be at least 30 days from Mo. 18 visit date

^ ALL participants attend Mo. 36 visit

6.0 Study Intervention

6.1 Procedures

All participants initially referred to the study will be screened with the anal cytology (Pap) test and, if applicable, will have HPV testing. Those tests will indicate those at highest risk, who should have HRA. Afterwards, the site study staff using a screening checklist will invite participants to participate in an additional screening that will include HRA and a biopsy to confirm a diagnosis of anal dysplasia (HGAIN). This screening visit will occur within three months of the baseline visit. For patients who have already been diagnosed with HGAIN prior to the screening visit, the screening and baseline visit can occur on the same visit date. All enrolled participants will then commence a schedule of study visits at the following times: Baseline (Day 0/visit 1), then months, 6, 12, 18, 24. 30 and 36. In addition, participants in the 'Immediate vaccine' arm will be seen at months 2 and 7. Participants in the 'Delayed vaccine' arm will also be seen at months 14, 19 and 48. At the screening visit, a physical exam will be done, along with an anal cytology Pap smear. Demographic information (age, sex, ethnicity), HIV information (year of diagnosis, HIV risk factor, treatment details), and a detailed sexual history will be collected in the 'Patient Intake Questionnaire'. After Screening, all regular study visits will include a focused health history and targeted physical examination, where clinically indicated (details below). At the Baseline, month 6, 12, 18, 24, 30, 36 and month 48 visits, a 'clinical questionnaire' will be administered to collect information on the participant's general health status, anal and sexual health, as well as participant acceptability and perceptions post anal cytology Pap smear, HRA, and treatment. This will be administered via REDCap and a link will be sent to the email address that the participant will provide. The presence, duration and intensity of symptoms such as pain (perianal, intra-anal, abdominal), discomfort, bleeding, discharge and fever will also be documented as well as any other adverse events.

In addition, the Baseline, Mo. 7, Mo.24, and Mo.36 visits for the Immediate arm participants will also include biologic sampling for HPV deoxynucleic acid (DNA) and HPV typing via swabs of the anal canal. Similarly, the Mo.12, Mo.19, Mo.36 and Mo.48 visits for the Delayed arm participants will include the HPV DNA/genotyping swabs. Polymerase chain reaction (PCR) will be performed via amplification of a fragment of the *L1* gene following DNA extraction, and the HPV genotyping will be performed using a Luminex-based system. Each regular study visit (except Mo2, Mo7, Mo14 and Mo19) will also include an examination of the anogenital areas as per the usual standard of care (which includes HRA with cytology and biopsies if applicable) to determine the presence of any anal lesions consistent with HPV. If these are present, the site investigator will treat with EC (electrocautery ablation).

All of the data collected during study visits will be abstracted to a case report form (CRF) by delegated research staff. Detailed descriptions on how to complete the CRFs will be available in the study instruction manual, which will be provided to the study sites.

Participant retention will be addressed in a number of ways. Local study site staff will ensure participant appointments are booked appropriately and conveniently, and will provide reminder calls to all participants prior to appointment days. If appointments are missed, efforts will be made to book a make-up appointment in a timely fashion. A mini-newsletter with study updates will be provided to all study sites on an annual basis.

6.2 Clinical Evaluations

Clinical evaluations, including health history and a physical examination will be performed at screening, baseline and all regular (Except mo. 2, 7, 14 and mo. 19 visits) follow-up visits.

The full health history at Screening will include:

- HIV-specific history, including date of diagnosis, risk factor for acquisition, and combination antiretroviral treatment history;
- Past medical history;
- Current and recent medications;
- Allergies;
- Immunization history;
- Smoking history, alcohol use, and other recreational drug use;
- Sexual history, including number and sex of sexual partners, types of activities (e.g. anal-receptive);
- Family history (particularly of malignancies of the anal canal, head and neck, or genital [penile, vulvar, cervical] areas); and,
- Review of systems.

The physical examination at Screening will include:

- Head and neck exam, including oral exam and lymph node exam;
- Genitourinary exam, including examination of perianal area;
- Anal exam, including a digital anorectal exam (DARE) and HRA;

The expectation is that both the health history and the physical examination will incorporate all of the above-mentioned components when done at the initial visit (Screening). However, these assessments at subsequent visits will be tailored to a more focused, less exhaustive format based on participant signs & symptoms (i.e. ensuring that any changes are noted, updating information such as medications, etc.) based on clinician discretion of the site investigator (henceforth called '***focused*** health history' and '***targeted*** physical examination').

6.3 Ablative Therapies

The ablative treatment modality in this study will be Electrocautery (EC). In EC treatment, the area of interest is anaesthetized with an injection of 2% lidocaine. The EC blade is passed down the anoscope to make contact with the lesion. The lesion is ablated using a gentle brushing technique, and the dead tissue is then removed with forceps or via blunt dissection with the anoscope, down to the submucosa. Hemostasis is then achieved with the EC device.

6.4 Laboratory Evaluations and Specimen Collection

No routine bloodwork will be collected for this study, with the exception of the HPV antibody levels described below. At each study visit, we will ask participants for a self-report of their most recent CD4 cell count and HIV RNA (i.e. viral load). If a participant does not know these results, we will retrieve them from the electronic medical records or patient charts, if available.

At Baseline, month 7 (one month after vaccination), month 24, month 36 for the Immediate arm, one swab from the anal canal will be collected for HPV DNA and HPV genotyping. Similarly, one anal swab will be collected for HPV DNA and genotyping at month 12, Month 19 (one month after vaccination), month 36 and 48 for the Delayed arm. Anal swabs will be collected for research purposes and sent to an external lab for analysis.

For the 'Immediate vaccine' arm, HPV antibody testing will be performed at Baseline, months 7 (primary outcome check; four weeks after final vaccine dose), and again at month 12, 24 and 36. For the 'Delayed vaccine' arm, HPV antibody testing will be performed at month 12, 19, 24, 36 (primary outcome check; four weeks after final vaccine dose) and again at month 48. Vaccine type epitope-specific neutralizing anti-HPV antibodies will be analyzed with a proprietary competitive Luminex immunoassay by the study funder (Merck). The techniques behind this assay has been previously published [39,40]. A blood sample will be collected for HPV antibody testing and shipped to the laboratory affiliated with Merck for processing and analysis. This laboratory is Q2 Solutions, LLC as arranged by Merck Canada; the serum samples will be collected by 2 study sites in Toronto and Vancouver for HPV Antibody testing.

6.5 Alternate Methods - Due to the COVID-19 Pandemic

Researchers have an ongoing ethical obligation to bring to participants' attention any changes to the clinical trial that may affect them. Thus, the appropriate study site staff shall disclose changes to the risks or potential benefits of the research. This includes the alternate methods used for the completion study visit assessments in order to minimize risk and exposure to COVID-19. This includes masking and physical distancing measures.

To minimize the risk and maximize the safety of study participants during the COVID-19 pandemic, the study procedures will be conducted in compliance with the guidance notes/memos issued by the institutional, ethical, and health regulatory bodies on clinical research operations and clinical trial management. Certain study visit procedures will be completed remotely with a virtual visit (either by phone call or videoconferencing via "Zoom for Healthcare" or similar secure platform), if possible, and upon the permission received from the participant and the collection of their personal email address and/or phone number. The participant will be well-informed on the risks associated with attending an in-person visit as well as the completion of study visit procedures via a virtual visit. Virtual visits will be conducted when necessary and feasible, and sufficient to assure the safety of trial participants. Procedures and assessments that can be completed remotely or during a virtual visit include obtaining fully informed consent, completing clinic

questionnaires (online), data collection of demographic information, health history, adverse event review, concomitant medication review, return and review of completed vaccine diaries and honorarium payment via bank e-transfer. Other procedures such as vaccine dose administration, physical exam, biospecimen collection, HRA, anal cytology and biopsies, and ablative treatment will require an in-person visit.

Documentation of the nature of alternate approaches to obtain consent, complete assessments (missed or completed) or visits (e.g. missed study visits or study discontinuations due to COVID-19) will be noted. This will include details on the specific limitations that might be imposed by COVID-19; these might lead to the inability to perform some of the protocol-specific assessments.

7.0 Study Visits

7.1 Summary of Study Visits

Details for each study visit are listed in subsequent sections. Section 5.4 outlines the participant timeline and visit details. The following is a snapshot summary of key study events:

- Consent: Screening visit
- Anogenital swabs for HPV DNA and genotyping: Screening and month 36 for all participants and an additional swab at Baseline, month 7 and 24 for the Immediate arm and month 12, 19 and 48 for the Delayed arm.
- A physical examination and history (Patient-intake questionnaire) will be done at the Screening visit.
- Focused history and targeted physical examination (only if clinically indicated): Baseline, month 6, 12, 18, 24, 30, 36 (and 48 for Delayed arm only).
- High-resolution anoscopy, anal cytology and biopsies: Screening, baseline, month 6, 12, 18, 24, 30, 36 (and 48 for Delayed arm only).
- Ablative therapy (EC): Done at Screening and Baseline and as needed (if participants develop recurrence of HGAIN, they will be offered re-treatment with EC ablation).
    - In order to accurately assess the primary outcome, all instances of anal lesions with associated biopsies and treatment will be captured from time of participant enrolment to final study visit (Mo.36 for Immediate arm, Mo.48 for Delayed arm). Instances that occur outside regular study visits will be captured through participant self-report, review of participant medical charts, or Unscheduled visits in some cases.
- Vaccine administration and safety check via vaccine diary and follow-up contact with participant (telephone calls, emails, or texts as appropriate): Baseline, months 2, 6 for the 'Immediate vaccine' arm; months 12, 14, 18, for the 'Delayed vaccine' arm.
- Anti-HPV antibodies and antibody quantification: Baseline, months 7, 12, 24, 36 for 'Immediate vaccine' arm; Baseline, months 12, 19, 24, 36, 48 for the 'Delayed vaccine' arm.
- Study end: month 48.

7.1.1 Screening Visit – Part I

Pap Test/Cytology

This will take approximately half an hour, and consist of the following:

- Explanation of study protocol
- Assess participant eligibility for screening portion of study
- Informed consent
- Collection of demographic information (Patient Intake Questionnaire)
- Digital anal examination
- Anal swab for cytology Pap smear testing

7.1.2 Screening Visit – Part II

This will take approximately one hour, and consist of the following:

- Ongoing assessment of informed consent/assent
- Explanation of study protocol
- Completion of Patient Intake questionnaire health history and physical examination.
- High-resolution anoscopy with anal cytology and biopsies of suspicious lesions.
- Ablative therapy for suspicions lesions if required
- Assess eligibility for treatment and entry into the vaccine study.

7.1.3 Baseline Visit (Day 0; Visit 1; within 3 months of screening visit; vaccination #1 for 'Immediate vaccine' arm)

This visit will take approximately two hours, and consist of the following:

- Ongoing assessment of informed consent/assent
- Randomization
- Completion of clinical questionnaire
- Focused health history and targeted physical examination
- Blood for HPV antibody testing in Immediate arm participants.
- Review of HGAIN biopsy results from screening visit
- Anal swab for HPV DNA/genotyping for Immediate arm participants.
- If applicable (as suggested by the anal Pap and HPV testing on that swab), high-resolution anoscopy with ablative EC therapy (i.e. electrocautery).
- Review of vaccination and determination of contraindications
- Administration of dose #1 of 9-valent HPV vaccination (with 15-minute post vaccination observation) for participants in 'Immediate vaccine' arm.
    - Review of 5-day vaccine diary and instructions on completion
    - Follow-up contact for 14 days (+/-2 days, depending on signs & symptoms) following vaccine dose to assess for adverse events

7.1.4 Visit 2 (month 2; vaccination #2 for 'Immediate vaccine' arm ONLY)

This visit will take approximately 45 minutes, and consist of the following:

- Ongoing assessment of informed consent/assent
- Review of vaccination administration

- Administration of dose #2 of 9-valent HPV vaccination (with 15-minute post vaccination observation) for participants in 'Immediate vaccine' arm.
    - Review of returned 5-days vaccine diary
    - Issue a new 5-day vaccine diary and review instructions
    - Follow-up contact for 14 days (+/-2 days, depending on signs & symptoms) following vaccine dose to assess for adverse events

7.1.5 Visit 3 (month 6; vaccination #3 for 'Immediate vaccine' arm)
This visit will take approximately 45 minutes, and consist of the following:

- Ongoing assessment of informed consent/assent
- Focused health history and targeted physical examination (only if indicated)
- Completion of clinical questionnaire
- High-resolution anoscopy with anal cytology
- Collection of biopsies with ablative therapy if clinically indicated
- Review of vaccination administration
- Administration of dose #3 of 9-valent HPV vaccination (with 15-minute post vaccination observation) for participants in the 'immediate vaccine' arm.
    - Review of returned 5-days vaccine diary
    - Issue a new 5-day vaccine diary and review instructions
    - Follow-up contact for 14 days (+/-2 days, depending on signs & symptoms) following vaccine dose to assess for adverse events

7.1.6 Visit 4 (month 7; seroconversion check for 'Immediate vaccine' arm ONLY)
This visit will take approximately 30 minutes, and consist of the following:

- Ongoing assessment of informed consent/assent
- Anal swab for HPV DNA/genotyping
- Blood for HPV antibody testing for the 'Immediate vaccine' arm.
- Adverse event monitoring

7.1.7 Visits 5,7 and 9-11 (months 12, 18, 24, 30, 36; follow-up visits)
These visits will each take approximately half an hour, and consist of the following:

- Ongoing assessment of informed consent/assent
- High-resolution anoscopy with anal cytology
- Collection of biopsies with ablative therapy if clinically indicated
- Focused health history, targeted physical examination (only if indicated) and completion of clinical questionnaire
- Adverse event monitoring

7.1.8 Visit 5 (month 12; vaccination #1 for 'Delayed vaccine' arm)
In addition to the procedures outlined in Section 7.1.7 for participants in both study arms for Visit 5, the following will be performed:

- Blood for HPV antibody testing for participants in both arms
- Anal swab for HPV DNA/genotyping for participants in Delayed arm
- Review of vaccination administration and determination of contraindications for participants in the Delayed arm

- Administration of dose #1 of 9-valent HPV vaccination (with 15-minute post vaccination observation) for participants in 'Delayed vaccine' arm.
    - Review of 5-day vaccine diary and instructions on completion
    - Follow-up contact for 14 days (+/-2 days, depending on signs & symptoms) following vaccine dose to assess for adverse events

7.1.9 Visit 6 (month 14; vaccination #2 for 'Delayed vaccine' arm ONLY)
In addition to the procedures outlined in Section 7.1.7 for participants in both study arms, the 'Delayed vaccine' arm will have the following performed:

- Ongoing assessment of informed consent/assent
- Review of vaccination administration
- Administration of dose #2 of 9-valent HPV vaccination (with 15-minute post vaccination observation) for participants in 'Delayed vaccine' arm.
    - Review of returned 5-days vaccine diary
    - Issue a new 5-day vaccine diary and review instructions
    - Follow-up contact for 14 days (+/-2 days, depending on signs & symptoms) following vaccine dose to assess for adverse events

7.1.10 Visit 7 (month 18; vaccination #3 for 'Delayed vaccine' arm)
In addition to the procedures outlined in Section 7.1.7 for participants in both study arms for Visit 7, the 'Delayed vaccine' arm will have the following performed:

- Review of vaccination administration
- Administration of dose #3 of 9-valent HPV vaccination (with 15-minute post vaccination observation) for participants in 'delayed vaccine' arm.
    - Review of returned 5-days vaccine diary
    - Issue a new 5-day vaccine diary and review instructions
    - Follow-up contact for 14 days (+/-2 days, depending on signs & symptoms) following vaccine dose to assess for adverse events

7.1.11 Visit 8 (month 19; seroconversion check for 'Delayed vaccine' arm ONLY)
This visit will take approximately 30 minutes, and consist of the following:

- Ongoing assessment of informed consent/assent
- Blood for HPV antibody testing for 'Delayed vaccine' arm.
- Anal swab for HPV DNA/genotyping.
- Adverse event monitoring

7.1.12 Visit 9 (month 24)
In addition to the procedures outlined in section 7.1.7 for participants in both study arms, these assessments will be done at Visit 9:

- Blood for HPV antibody testing for participants in both arms.
- Anal swab for HPV DNA/genotyping for participants in the 'Immediate' arm.

7.1.13 Visit 10 (month 30)
Only the procedures outlined in section 7.1.7 are conducted with participants in both study arms at this visit.

7.1.14 Visit 11 (month 36; final study visit for 'Immediate vaccine' arm)

In addition to the procedures outlined in Section 7.1.7 for participants in both study arms, these assessments will be done at Visit 11:

- Blood for HPV antibody testing for participant in both vaccine arms.
- Anal swab for HPV DNA/genotyping for participants in both vaccine arms.

7.1.15 Visit 12 (month 48; final study visit for 'Delayed vaccine' arm ONLY)

Participants in the 'Delayed vaccine' arm will have the following performed:

- Ongoing assessment of informed consent/assent
- High-resolution anoscopy with anal cytology
- Collection of biopsies with ablative therapy if clinically indicated
- Focused health history, targeted physical examination (only if indicated) and completion of clinical questionnaire
- Blood for HPV antibody testing
- Anal swab for HPV DNA/genotyping
- Adverse event monitoring

7.1.16 Unscheduled Visits

Unscheduled visits may be conducted with a participant at any time during the study period at the discretion of the Qualified Investigator for clinical safety or for the follow-up of AEs. Laboratory parameters may be measured and clinical evaluations may be performed as deemed clinically relevant by the Investigator.

If a participant has their dose of vaccination interrupted, or permanently suspended during the course of the study, they will be asked to return to the study clinic for an Unscheduled Visit if the Investigator deems it necessary to assess safety variables.

7.1.17 Procedures for Withdrawal

If a participant withdraws or is removed from the study for any reason prior to the completion of the study, the reason for, date of the discontinuation, and the date of the last dose of vaccination (where applicable) must be recorded in the participant's file and the appropriate section of the eCRF.

At the time of withdrawal, every effort should be made to ensure that:

1. The participant attends a final study visit at which study procedures and evaluations will be performed per the discretion of the investigator based on the timing and specific details of the events that lead to the withdrawal, but should include the assessment of AEs. If the participant discontinues the study prior to receiving the full course of 3 vaccinations, they will continue to be followed in the clinic as per standard of care as long as they are willing to do so.
2. At minimum, study staff will make an appointment for safety follow-up visit(s) as required per the investigator's clinical judgement.

All premature withdrawals and their causes must be documented by the site investigator or designated study staff on the appropriate eCRF pages (e.g., Final Status, AE). Participants not completing the entire study should be fully evaluated whenever possible.

Any participant who discontinues participation due to an unresolved clinically significant AE will be followed until satisfactory clinical resolution is achieved and the AE documented in the eCRF regardless of disease severity. For all AEs that require the participant to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated per the Investigator's clinical judgement until final resolution or stabilization of the event(s). These visits will be entered into the eCRF as Unscheduled Visits. If a participant is withdrawn from the study due to study vaccination intolerability, an AE should be recorded **regardless of grade**.

7.2 Study Duration

The expected duration of the study from baseline to completion is 36 months for the immediate arm and 48 months for the delayed arm. Recruitment began in May 2023 and will be ongoing for at least 2 years. We anticipate that the last-recruited participant will complete in roughly 6 years.

8.0 Statistics

The Sponsor-Investigator and the HPV-SAVE team will be solely responsible for data analysis.

8.1 Definition of Analysis Populations

An intention-to-treat (ITT) analysis approach will be taken in this study. The intention-to-treat population will include those participants who were enrolled in the study and received at least one dose of the vaccination.

8.2 Baseline data

Demographic and clinical characteristics will be described with frequencies and proportions for categorical variables, means and standard deviations for normally distributed continuous variables, and medians and interquartile ranges for non-normally distributed continuous variables.

8.3 Primary outcomes

The primary efficacy outcome of the study will be the proportion of participants in each arm with at least one reoccurrence of biopsy-proven HGAIN (AIN-2/3) during 36 months following successful treatment of HGAIN. The overall proportion of participants with recurrence will be reported, along with 95% confidence intervals (CI).

The primary analysis will be a two-sample test of proportions of the proportions of patients experiencing recurrence by month 36 between intervention arms. Logistic regression will be used assess the effect of treatment on the odds ratio on recurrence of all lesions by 36 months, after adjusting for patient characteristics at enrolment.

The primary safety outcome of the study will be the frequency of vaccine-related adverse events. The proportion and 95% confidence intervals of adverse events by grade and treatment arm will be calculated.

8.4 Secondary outcomes

A secondary efficacy outcome of the study is the proportion of participants with GMT of HPV antibody for each vaccine type above a pre-specified cutoff (presented in Section 2.3) at month 7 ('immediate vaccine' arm) or month 19 ('delayed vaccine' arm). More specifically, this is defined as a participant who is seronegative at study screening and baseline (i.e. no detectable HPV antibodies or GMT of antibody below the cut-off), and seropositive at month 7 or 19 (i.e. GMT antibody level above the cut-off). Separate analyses will be performed for each HPV vaccine type (i.e. 6, 11, 16, 18, 31, 33, 45, 52, and 58), and will be analyzed by serostatus (i.e. HPV-type +/-) and HPV DNA status (i.e. HPV type DNA +/-) based on the screening and baseline results of this testing. The overall proportion of participants achieving seroconversion will be reported, along with 95% CI.

Predictors of seroconversion against HPV vaccine types in the study population will be identified using logistic regression. Univariate analyses will be performed to determine which variables to include in the multivariable analysis. Variables examined will include: age, ethnicity, use of cART, CD4 count, viral load, comorbid hepatitis C or hepatitis B infection, HIV risk factor, and number of lifetime sexual partners.

HPV detection will be done from anal canal swabs. We will compare loss of carriage of vaccine HPV types in the immunized versus unimmunized groups at similar time points. This will indicate the "vaccine effect". Indeed, since 90% of participants are expected to have high risk HPV carriage at any time point, a reduction in such carriage after immunization could be attributed to a "vaccine effect".

8.5 Missing data

Sensitivity analyses using "worst-case scenario" will be performed in the event that missing data exceeds 5%.

8.6 Sample Size Considerations/Justifications

Based on previous data (discussed in 'Background' section) examining recurrence rates of HGAIN in MSM, the observed rate of HGAIN recurrence for unvaccinated individuals following ablative therapy ranged from roughly 60-90% within two years. We will conservatively estimate a HGAIN recurrence rate of 70% in unvaccinated MSM at 36 months. If the true recurrence rate for vaccinated participants is 50%, we will require a sample size of 103 participants in each arm (total of 206 participants overall) in order to reject the null hypothesis that the recurrence rate for vaccinated and unvaccinated MSM is equal, with power of 80%. Assuming a dropout rate of 10%, our revised sample size is 114 participants per arm (228 participants in total).

9.0 Adverse Event Reporting

9.1 Data Safety Monitoring Committee

An independent Data Safety and Monitoring Committee (DSMC), provided by The CIHR Canadian HIV Trials Network (CTN), will be involved with the study, comprised of members with expertise in the content area and in the conduct of clinical trials. All

members will be independent of the proposed study, the study investigators, and Sponsor-Investigator. Safety data will be submitted for review at regular biannual DSMC meetings. The DSMC has the ability to recommend study discontinuation if any study data shows evidence of a potential safety risk to participants. The DSMC will provide their recommendations in a written report to the study Sponsor-Investigator. In the event that a serious adverse event or death occurs outside regular meeting dates, the DSMC will be notified and involved as appropriate.

9.2 Harms and Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant, following the administration of a study medication/intervention, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) study medication/intervention, whether or not the AE is related to the medicinal (investigational) study medication/intervention

At the Screening visit, all trial participants will be advised to contact the site investigator or coordinator if any of the following occur: newly diagnosed conditions or illnesses, worsening or change in pre-existing conditions, or any other medically-significant health changes (as deemed by the site investigator). During each follow-up visit with a participant, information on such adverse events (AEs) will be gathered and documented accordingly. As previously described, AE data will also be collected via self-reported vaccine diaries for five days and follow-up contact (phone call, email, or text as applicable) between the participant and research team following each vaccination. In addition, AE data will also be collected following ablative therapies. Adverse events will be followed up until resolution or up to 30 days following each vaccination or ablative therapy. Note that instances of anal lesions (of any kind) will not be recorded as AEs but tracked and documented separately for the purpose of assessing the primary outcome. Any occurrence of anal cancer will be considered an SAE and also a withdrawal criteria All adverse events will be graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables) as mild, moderate, severe or life-threatening, and details including associated symptoms, duration, and treatments will be documented. Site Investigators must sign off on the severity and relatedness/causality of all adverse events based on temporal relationship and their clinical judgment. Relatedness will be determined to be definitely related, probably related, possibly related, unlikely to be related, or not related to vaccine.

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to Investigational Product (FMT or placebo) administration and cannot be explained by concurrent disease or other products or chemicals. The response to withdrawal of the product (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the Investigational Product, is unlikely to be attributed to concurrent disease or other products or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an adverse event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to Investigational Product administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other products or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not related: The AE is completely independent of Investigational Product administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician

Adverse events that are assessed and determined not to be related to study procedures or vaccine will be recorded but will not be reported to REB or other regulatory authority.

9.3 Serious Adverse Events (SAE)

A SAE is defined as an AE occurrence meeting one of the following criteria:

- Death during the period of protocol-defined surveillance
- Life-threatening event (defined as participant at immediate 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)
- In-patient hospitalization of prolongation of existing hospitalization during the period of protocol-defined surveillance
- Results in a congenital anomaly or a birth defect
- Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in one of the above outcomes, may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization.

Participants will be monitored during the study period for SAEs. If an SAE is ongoing at the time a participant discontinues/completes the study, the SAE will be followed until the Investigator and the independent reviewer agree that the event is satisfactorily resolved, becomes chronic, or that no further follow-up is required.

9.3.1 SAE Reporting

Study sites are required to report all SAEs occurring during the course of the study to Dr. Grennan or Dr. Weiss within 24 hours of the site becoming aware of the event.

UHN Participant SAEs will be reported to:

Dr. Troy Grennan

Attention:	Dr T. Grennan
Phone:	+ 1 604-707-5606
Fax:	+ 1 604-707-5604
E-mail:	Troy.grennan@bccdc.ca

BCCDC Participant SAEs will be reported to:

Dr. Edward Weiss

Attention:	Dr E. Weiss
Phone:	+ 1 416-340-8172
Fax:	+ 1 416-340-4890
E-mail:	edward.weiss@uhn.ca

All additional follow-up evaluations must also be reported as soon as possible in the same manner. All SAEs will be followed until the site Investigator (or sub-investigator) and independent reviewer agree that the event is satisfactorily resolved, becomes chronic, or no further follow-up is required.

The Sponsor-Investigator will ensure that all participating study sites are notified of any SAEs that are definitely, probably or possibly related to the intervention. Each Qualified Investigator is responsible for ensuring that their local Research Ethics Board (REB) is notified of any SAEs as per the local requirements.

The Sponsor-Investigator will be responsible for reporting in an expedited manner, any serious unexpected adverse drug reactions to Health Canada within the required timelines:

a. Where it is neither fatal nor life-threatening, within **15 days** after becoming aware of the information;

b. Where it is fatal or life-threatening, within **7 days** after becoming aware of the information. Within 8 days after having initially informed Health Canada of the fatal or life-threatening ADR, submit as complete a report as possible. Follow-up reports of fatal or life-threatening reactions **must** include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs.

10.0 Data Handling

10.1 Data Handling and Record Keeping

For clinical trials, all records and documents pertaining to the study will be retained by the study trial site at UHN for at least 15 years from the completion of the study, and will be available for inspection by the Sponsor and/or the Regulatory Agencies.

11.0 Randomization

Randomization will be stratified by site with permuted blocks of random size. The random allocations will be computer-generated by a statistician unassociated with the study. The allocations will be loaded into an online web-based randomization system at the CIHR Canadian HIV Trials Network national centre in Vancouver. The allocation system will be password protected, and each site will be given individual passwords to access the system. When a participant has been consented and is subsequently deemed eligible by the site investigator, delegated study site staff will interact with a web-based randomization interface and receive the participant's allocation to either the Immediate vaccination or the Delayed vaccination arm, in a 1:1 ratio. An automatic audit trail of all interactions will be recorded and will include the participant study identification number, the date and time of the randomization, and the allocated treatment arm.

12.0 Knowledge Translation

12.1 Dissemination Policy

The results of the trial will be disseminated in a number of ways. A summary of final results will be sent to all participants, site investigators and coordinators, and posted to the CIHR Canadian HIV Trials Network website, as well as on the website of our applicable study partners (e.g. Community AIDS Treatment Information Exchange (CATIE)). A variety of presentations at national and international conferences (including the Conference on Retroviruses and Opportunistic Infections [CROI], the International AIDS Conference, the International Papillomavirus Conference), as well as publications in high-impact journals (including Clinical Infectious Diseases, AIDS) are anticipated, and all authors will come from the pool of trial investigators and HPV-SAVE team members; no professional authors will be utilized. Official authorship guidelines have yet to be formalized. Whether or not the full protocol, the dataset and the statistical code will be made available publicly has yet to be determined.

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