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Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV): Design and methods for a randomized controlled trial

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Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV): Design and methods for a randomized controlled trial

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ABSTRACT

Introduction

Men who have sex with men (MSM) have an increased risk of human papillomavirus (HPV) infection and HPV-associated diseases, such as anal cancer and anogenital warts. A carrageenan-based lubricant has the potential to prevent HPV infection, thereby reducing the disease burden in this vulnerable population. This paper aims to describe the protocol for the Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV) study, an ongoing randomized controlled trial (RCT), evaluating 1) efficacy of a carrageenan-based personal lubricant in reducing type-specific anal HPV incidence and prevalence among sexually active MSM, 2) efficacy by HIV status, 3) safety and tolerability of the gel, and 4) participant adherence to the intervention.

Methods and analysis

The study is a randomized, double-blinded, placebo-controlled trial. Volunteer MSM 18 years and older are randomly assigned 1:1 to receive the treatment (a self-applied anal microbicide gel with carrageenan) or placebo (a self-applied placebo gel). At each visit, computerized questionnaires are used to collect data on sociodemographic and clinical variables, lifestyle, sexual behaviour, and the gels' safety and tolerability. At baseline and each follow-up visit (months 1, 2, 3, 6, 9, 12), nurses collect anal specimens tested for 36 HPV types (Linear Array Assay). HIV status is determined at baseline and 12 months. The primary outcome is incidence of type-specific anal HPV infection(s) undetected at baseline. Secondary outcomes are prevalence of type-specific anal HPV infection, safety, tolerability, and adherence. Data will be analysed using intention-to-treat and per-protocol approaches. Subgroup analyses by HIV status will be performed.

Ethics and dissemination

Ethics approval was obtained by the Research Ethics Boards of McGill University, the McGill University Health Centre (MUHC), Concordia University, and Centre Hospitalier de l'Université de Montréal (CHUM). Trial results will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number NCT02354144; Pre-results.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- First study to explore the efficacy of carrageenan as a topical microbicide for preventing anal HPV acquisition in MSM
- Randomized Controlled Trial design comparing carrageenan lubricant gel to placebo is optimal to evaluate the efficacy of carrageenan in MSM with and without HIV
- Due to design limitations, dosage efficacy will not be evaluated
- The exact time of HPV acquisition will be unknown

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INTRODUCTION

Background and rationale

Human papillomavirus (HPV) is one of the most common sexually transmitted infections worldwide.[1] A 2012 meta-analysis found that 93% of HIV-positive men who have sex with men[1] (MSM) and 65% of HIV-negative MSM are currently infected with HPV.[2] Recently, an updated meta-analysis reported an HPV prevalence for HIV-positive and HIV-negative MSM of 81% and 47%, respectively.[3] There is overwhelming evidence that persistent HPV infection with high oncogenic risk HPV types is the primary risk factor leading to pre-cancerous anal lesions.[4–13]

While the incidence rate of anal cancer is 1-2 per 100,000 per year,[14] the rate is 5.1 per 100,000 among HIV-negative MSM, and 45.9 per 100,000 among HIV-positive MSM, based on multinational data.[2] There is a lack of consensus on an anal screening strategy, and screening for high-grade lesions has not yet been shown to reduce the incidence of anal cancer.[15] The risk of other HPV-related lesions, such as genital warts, may decrease with condom use, but there is no consensus on whether condom use decreases the risk of HPV positivity.[16] Additionally, of the three current prophylactic HPV vaccines available, two are recommended for MSM[17] and offer protection from two (Gardasil®)[18] or seven (Gardasil 9®) high-risk HPV types.[19] There is thus a need for additional primary prevention measures.

Carrageenan was shown to effectively block HPV transmission in in vitro[20] and animal studies.[21,22] It is naturally derived from 3 species of red algae and has a long history of human use as a stabilizer and emulsifier.[23] The safety and acceptability of a carrageenan-containing microbicide gel was demonstrated.[24–26] Because of the high prevalence of HPV and the greater risk of anal cancer and its precursor lesions in MSM, compared to men in the general population, it is critical to determine whether a carrageenan-based lubricant can prevent HPV

[1] For brevity, this acronym reflects the term most commonly used in the biomedical literature on HIV and HPV. However, to be specific and consistent with modern, more appropriate usage the term denotes individuals assigned a male gender at birth who have sex with individuals assigned as male at birth. It excludes transfemales or individuals transitioning from male to female.

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transmission among this vulnerable group. Moreover, as carrageenan's primary mechanism of action against HPV may be affected by innate and adaptive immune responses,[27] it is essential to verify if similar efficacy is observed in men with and without HIV. The aim of this paper is to describe the protocol for the 'Lubricant Investigation in Men to Inhibit Transmission of HPV Infection' (LIMIT-HPV) study, an ongoing, phase IIB, placebo-controlled, double-blinded randomized clinical trial (RCT) to evaluate the effect of a carrageenan-based lubricant on anal HPV infections in MSM.

Study objectives

The primary objective is to evaluate the efficacy of carrageenan in reducing type-specific anal HPV incidence, i.e., in preventing incident infections by HPV types undetected at baseline in sexually active MSM. Secondary objectives are to: 1) evaluate the efficacy of carrageenan in reducing type-specific anal HPV prevalence, i.e., in accelerating clearance of existing infections in sexually active MSM; and 2) assess the safety and tolerability of the proposed gel and participant adherence to the intervention.

METHODS AND ANALYSIS

Study design

LIMIT-HPV is an exploratory, phase IIB, parallel group, block-randomized, placebo-controlled, RCT with 1:1 random assignment to the treatment (a self-applied anal microbicide gel with carrageenan) or placebo (a self-applied placebo gel) group. The trial was registered on clinicaltrials.gov (NCT02354144) on February 2016.

Patient and Public Involvement Statement

Prior to study initiation, a focus group was conducted to gather recommendations from 20 volunteer MSM and adapt our protocol accordingly. Participants answered a self-administered questionnaire, providing their perspective on sexual behaviour; lubricant and condom usage; candidate gels; partner's support and potential impact on compliance; sample collection; willingness to enroll in the trial, as well as other concerns and suggestions. The feasibility study in itself did not inform the research question, however, the trial design was directly impacted. For example, participants were asked about the maximum frequency they would be willing to

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have an anal specimen collected, which directly informed the frequency of testing in the actual RCT. Additionally, the question of whether the sample should be collected by a study nurse rather than self-collected was supported by 6/20 MSM, while 10/20 had no preference. Gel packaging was also adapted for their preferences. The recommended average monetary compensation to participate in the trial was $26.50 per visit.

Setting and recruitment

Participants are recruited at the participating clinical sites or via advertisements in various media – (classified ads on Kijiji, Craigslist, and Les Pacs; Facebook; Fugues magazine, Quebec's gay and lesbian magazine; McGill and Concordia Classifieds; an interview on McGill/Montreal CKUT Campus Community radio station; promotional videos; 'What's New' blurbs emailed to McGill students; study announcements emailed to Université de Montréal students; and class presentations) – and through printed promotional materials, including posters, business cards, posters, and button pins. Study recruitment began in February 2016 and study visits are conducted at the following clinical sites: MUHC, Clinique Médicale Urbaine du Quartier-Latin, Clinique OPUS, McGill Health Service Clinic, Concordia Health Services or at the Gerald Bronfman Department of Oncology at the Division of Cancer Epidemiology of McGill University.

Study population and procedures

Individuals are screened directly for eligibility at the clinical sites or prior to that over the telephone (Appendix 1). Alternatively, subjects interested in the study can first fill out an online, self-administered eligibility pre-enrollment questionnaire (Appendix 2). If eligible, they are contacted to confirm their eligibility and schedule the enrollment visit. Otherwise, they are emailed to thank them for their interest and explain their ineligibility.

Eligibility is based on the following criteria:

- men aged 18 or older,
- living in Montreal and planning to remain in the city for the next 12 months,
- having had receptive anal sex with one or more men during the previous 3 months and intend to continue being sexually active for the duration of their involvement in the study, irrespective of whether their sexual partner will change,

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- planning on having receptive anal sex with one or more men, but less than 50 different partners per year,
- understanding French or English,
- willing to follow study instructions and comply with follow-ups for 12 months,
- willing to do an HIV-test (for men who were never tested seropositive for HIV).

Exclusion criteria:

- participants must not be receiving treatment for anal or perianal condylomas or anal intraepithelial neoplasia lesions during the trial,
- must not have a known allergy or hypersensitivity to any of the ingredients in either gels.

Study procedures according to each visit are summarized in Figure 1. Eligible men attend an enrolment visit, where the research nurse obtains written, site-specific informed consent (Appendix 3 McGill site) and instructs the participant on proper gel use. A one-month gel supply is provided, and the first specimen is collected. The nurse also provides details about HPV infection and advice about condom use and sexual health (i.e., importance of condom use to prevent HIV and other STIs). At subsequent visits, additional bottles of gel are provided, and patients are reminded to use the gel.

Randomization and blinding

Once written informed consent is obtained and HIV status is confirmed, participants are randomized 1:1 to receive either a carrageenan-containing gel or a placebo gel. Intervention assignment occurs via a computer-assisted block randomization with randomly variable block sizes. Each participant is assigned an individual code for the duration of the study, which is used to match him to the study arm. The trial is double-blinded: participants, care providers, investigators, outcomes assessors are unaware of treatment allocation. To ensure blinding, the two gels and their containers look and feel almost identical. Additionally, four random product codes are assigned to the treatment gel and a different set to the control gel (eight in total) to minimize the risk of unblinding. The success of blinding is evaluated at 6 and 12 months by asking subjects to guess their assignment. If the majority guess correctly, it would suggest that blinding was ineffective.

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Intervention

The intervention and placebo gels used in this trial are two commercially available gels. The differentiating feature is that one gel contains carrageenan (intervention) and the other does not (placebo). Both gels are water-based, latex-condom compatible, clear, odourless, tasteless, and have similar viscosity. Both are packaged in a plastic bottle with a disk cap that can be operated with one finger, and must be applied prior to receptive anal intercourse (RAI) during the entire study period. Participants are instructed to dispense around 15 ml of the gel into the hand and apply directly to genital, anal, and condom surfaces prior to and as needed during RAI. When sexual activity ceases, the water-based formulation of the gel allows it to be easily removed with lukewarm water. Participants are asked to use the assigned gel for the entire 12 months of follow-up, independently of other methods of protection against STIs (e.g., condoms).

Adherence

To improve adherence, participants are provided with an unlimited gel supply until the end of the study. Up until April 2019, a monetary compensation of $25/visit was provided to each participant. This amount was since increased to $50/visit to better reflect the market for compensation in clinical research and help retain participants.

care Concomitant

The nurse inform unvaccinated individuals that the HPV vaccine has now been approved for men between 9 and 26 years of age, and remind them that protection is prophylactic and restricted to 9 vaccine-target types. In addition to the required intervention gel, we recommend condom use for the prevention of HIV and other STIs. Condoms are easily accessible: many community organizations in Montreal such as REZO, a community-based organization dedicated to health promotion and prevention of HIV/AIDS and other STIs, already provide condoms free of charge as a public health intervention. We also offer participants with latex allergies non-latex condoms free-of-charge that are compatible with the study gels.

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Sample size

We used data from the Montreal HIPVIRG cohort study of MSM living with HIV[28] and a multinational meta-analysis representing both MSM subgroups[2] to inform our calculation of sample size. The reported prevalence in the HIPVIRG population[28] was very similar to studies that were conducted outside of Montreal in MSM living with HIV [2], justifying adopting incidence data from MSM without HIV from settings outside of Montreal. The technique of Dupont and Plummer was used to estimate the hazard rate of acquisition.[29] Among HIV-negative MSM, we estimated a conservative preventive effect size of 50% based on the expert opinion of Dr. John Schiller who discovered carrageenan's inhibitory properties (personal communication).[20] We expect a lower effect size of 30% among HIV-positive MSM, as carrageenan's primary inhibition mechanism relies on the immune response. The power calculations were separately tailored to satisfy our primary endpoint in each MSM population; however, if results are homogeneous across groups, we will consider pooling results to improve the precision of our estimates. Additionally, we specified 80% power to evaluate our primary objective with a type 1 error of 0.05 and 2-sided hypothesis. Assuming an incidence proportion of 30% at 12 months among HIV negative MSM[2] and accounting for 10% loss to follow-up, the sample size required for an effect size of 50% was calculated to be 270. Similarly, assuming an 85% incidence of HPV infection at 12 months among HIV-positive MSM[2] and accounting for 10% loss to follow-up, the estimated sample size required for an effect size of 30% was calculated to be 107. Hence, recruiting 380 participants (110 HIV-positive and 270 HIV-negative) would ensure sufficient power at the end of follow-up to assess the study's objectives. With the high frequency of new sex partners among MSM in a similar study by our group,[28] a 1-year follow-up period would be sufficient to allow HPV exposure opportunity and evaluate compliance.

Data collection

The initial visit takes approximately 30 minutes, while all subsequent follow-up visits (1, 2, 3, 6, 9 and 12 months) require about 20 minutes each. Men are asked to abstain from receptive anal sex and gel use 48 hours before specimen collection to minimize the risk of contamination.[30]

Computerized questionnaire

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Participants complete a self-administered baseline questionnaire at enrolment, and six follow-up questionnaires (Appendices 4 and 5, respectively). These measure HPV risk factors, compliance, and monitor the gels' safety and tolerability. Between follow-up visits, participants are asked to log into a secure web module at least once a week to answer questions on daily sexual activities, condom and study gel use, and adverse events (AE). To minimize recall bias, information can only be updated for the past 7 days (incomplete surveys expire after a week). Web-based diaries have been shown to be effective for logging sexual activities, and superior to questionnaires completed during visits for reducing recall bias.[31] This ensures high compliance and improves data quality. Responses are employed to evaluate adherence and assist in developing future studies.

Reporting AEs

To gauge the severity of AEs related to the study intervention, we refer to the Rectal Genital Grading Table for Use in Microbicide Studies[32] and Male Genital Grading Table for Use in Microbicide Studies[33]. If a stable, chronic condition is noted in the enrolment medical history questionnaire, but does not exacerbate during the trial, symptoms are recorded in the AE report but are not considered to be attributable to the gel. Subjects are advised to promptly notify the nurse of any AE; the event is documented, and the participant is triaged and treated at the discretion of the study physicians. Nonetheless, should subjects fail to immediately report an AE, they are also asked about any recent medical visits/AEs at each follow-up visit in the questionnaire.

Anal sample collection

HPV infection status is assessed by testing anal specimens. Trained study nurses collect specimens according to the Protocol for Anal Swab Collection (Appendix 6).[28] The swab sample is immediately preserved in PreservCyt and kept at 4°C pending transfer to Dr. Coutlée's laboratory, a WHO-accredited HPV diagnostics centre. Samples are batched and transported every 2-3 months.

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HPV DNA detection and typing

The swab sample is subject to centrifugation at 13,000*g* for 15 min at 22°C; the supernatant is discarded, and the pellet is resuspended in 300µL of 20mmol/L Tris buffer (pH 8.3). DNA is purified using a Master-Pure Kit (Epicentre) and tested in each polymerase chain reaction (PCR) assay.[34] HPV detection and typing is done via the PGMY PCR protocol coupled with the Linear Array method, commercially available from Roche.[35] This test permits testing and typing for 36 different genital HPV types.[35] These types can be categorized into 3 alphapapillomavirus subgenera based on oncogenicity and tissue tropism: subgenus 1 includes low oncogenic risk types (HPVs 6, 11, 40, 42, 44, 54), subgenus 2 includes high oncogenic risk types (HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82), and subgenus 3 includes mostly commensal types (HPVs 61, 62, 71, 72, 81, 83, 84, 89).[36–39]

HIV testing

For participants who reported being HIV-negative, the nurse performs a rapid HIV test at baseline and at 12 months, as is standard of care in high risk populations (Appendix 7). If positive, the participant is referred immediately to Dr. de Pokomandy at the MUHC to ensure rapid engagement with HIV care. For HIV-positive participants, a brief chart review is done at 0, 6 & 12 months to collect information on CD4 count, HIV viral load, and current antiretroviral regimen.

Loss to follow-up

Discontinuing participation of a study subject occurs if the participant voluntarily withdraws from the trial, or has AEs, illness, or other medical conditions determined by a physician to be serious enough to terminate his involvement in the study. Loss to follow-up is described as failure to reach a participant for a follow-up visit 6 months post-randomization, or the potential for a participant to jeopardize the study's integrity through protocol noncompliance.

Outcome measures

The primary outcome is presence of a newly detected anal infection of a specific HPV type(s) in an individual who was negative for that HPV type(s) at enrolment. The secondary outcome is clearance of type-specific anal HPV infections found at baseline. Analyses will be conducted for a conservative (one negative HPV result after a positive result) and liberal (two consecutive

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negative results after a positive result) definition of clearance. Other secondary outcomes include participant adherence and AEs reporting.

Data management

Study and data management are facilitated through the use of a secure, password-protected web-based database to record and manage study procedures. The database is used to record participant and clinic visit information, plan visits, and export data. It is only accessible from specific IP addresses. A coded numeric system is used to identify subjects. All data, including but not limited to records, case report forms, and laboratory results remain confidential and stored in a secure location. Research staff are the only individuals with access to these personal documents. They are available to the study sponsor or participating regulatory agencies upon request. For quality control, data are downloaded from the server each month and checked for possible errors. Data management is done using SAS v9.4 (SAS Inc., Cary, NC, USA). Any missing data will be handled by multiple imputations if appropriate.

Data analysis

Analyses will be conducted separately among MSM with and without HIV, and later pooled if appropriate. These will use intention-to-treat (i.e., including all participants who were randomized and received at least one-month's supply of gel) and per-protocol (i.e., including only "adherent" participants who complied with the protocol) approaches. Because of randomization, we expect the rates of type-specific HPV infections to be comparable between study arms at enrolment.

Primary aim 1 (prevention)

Carrageenan's efficacy will be evaluated by testing the null hypothesis of no difference in time to anal type-specific HPV incident infection between treatment groups using the log rank test. Time to HPV infection will be defined as the difference in days between an incident HPV detection date and time zero at enrolment. We will use Cox proportional hazards regression to estimate the hazard ratio and 95% confidence interval of HPV infection for treatment versus placebo. If the proportionality assumption is not met or the hazard ratio changes over time, we will fit a discrete-time hazards model.[40]

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A sensitivity analysis will be conducted restricting to the most adherent participants in terms of gel usage. Adherence will be calculated as the number of times the gel was used during RAI divided by the number of RAIs reported in the same interval. A participant will be considered adherent if he reported, as recommended, gel use at least >50% of the time prior to every act of intercourse. Additional analyses will allow for time-varying adherence, defined as adherence since the last administered questionnaire.

Secondary aim 1 (clearance)

Time-to-event analysis techniques will be used to measure type-specific clearance of HPV infections present at enrolment, according to the intervention. Time to clearance and hazard ratios of clearance will be calculated as above.

Secondary aim 2 (Safety, tolerability, and adherence)

Safety and tolerability of the interventions will be evaluated using the AE reports from both groups. For each participant, mean adherence will be calculated for the time period between two consecutive visits and for the whole follow-up period, and it will be compared between the intervention and placebo groups using a t-test. If adherence is not normally distributed, median adherence will be compared between groups using the Mann-Whitney test. As mentioned previously, adherence will also be evaluated as a binary variable and compared between groups using the chi-square test, for each interval and overall.

Monitoring

An independent data safety monitoring board oversees the trial to ensure that it is conducted in accordance with the ethical principles of good clinical practice. The board will review the results of the interim analysis and make recommendations regarding safety concerns, and/or suspension or early termination of the study (e.g., unequivocal evidence of efficacy). The same board members also oversee the Carrageenan gel Against Transmission of Cervical HPV (CATCH) RCT, which is similar in design to LIMIT-HPV, however it looks at the efficacy of a carrageenan gel among heterosexually active women.[41]

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ETHICS AND DISSEMINATION

The study received ethical approval by institutional review boards of McGill University (A10-M98-14B), MUHC (2016-1434, 15-332-MUHC), Concordia University (30006074), and Centre Hospitalier de l'Université de Montréal. Protocol amendments are submitted and approved by these boards. This is the 7th study protocol version, last revised January 30th, 2019. When 50% of the targeted population (380 MSM) are recruited, an interim analysis will be conducted. Reports of trial findings – in the form of abstracts and manuscripts to be submitted, respectively, to peer-reviewed journals and conferences – will be presented according to the CONsolidated Standards of Reporting Trials (CONSORT) statement.[42] The co-investigators involved in the study will assist in dissemination of research findings directly to health clinics and the MSM community.

DISCUSSION

Presently, there is no effective way to treat anal HPV infections. With the potential for broad-spectrum anti-HPV activity, carrageenan could be a useful adjunct to HPV vaccination as a primary means of preventing HPV infections. Given the high burden of HPV infections in the MSM community, regular application of a carrageenan-based lubricant could be a cost-effective preventive approach, especially considering that most MSM regularly use lubricants for anal sex. Furthermore, treatments for condyloma and high-grade lesions are costly and often need to be repeated, as the recurrence rate is very high (particularly among people with HIV).[43] Also, vaccination is generally only maximally effective at preventing infection if administered prior to becoming sexually active.[44]

To the best of our knowledge, the LIMIT-HPV study is the first to test carrageenan against anal HPV infections. Its main strength is the blinded randomized trial design. Additionally, considering HIV positive and negative MSM would allow for the evaluation of the gel's efficacy in both groups. There are limitations that should be acknowledged. An evaluation of dosage efficacy is not possible, as we do not collect information on the exact amount of gel used. Also, although daily measurement of HPV status would have produced the most reliable estimation of infection time (allowing the detection of transient infections), the current frequency of anal swab samples was selected based on acceptability by participants and financial feasibility. HPV incidence is consequently interval-censored. That is, infection date occurs sometime between the

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last negative and the first positive test, but the exact date is unknown. However, as the time interval between each visit is relatively short, the interval would represent an appropriate approximation.

The LIMIT-HPV study may show a similar protective effect as was demonstrated in an interim analysis of a related study (CATCH-RCT) conducted by our team. A reduction in the risk of incident HPV infection among participants randomized to the carrageenan gel compared to the placebo gel was demonstrated, and importantly, the gels appeared safe: none of the reported AE were attributed to the gels.[41] If efficacy of the carrageenan gel is demonstrated, the current trial has the potential to improve the health of individuals in the MSM community by providing protection against all HPV genotypes, and ultimately reducing the risk of HPV-associated diseases in this high risk group.

Acknowledgements

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Author's contributions

ELF, AdP, FC, and PPT conceived and designed the study. JT contributed to the grant application writing. MZ managed the study. CL drafted the manuscript under the supervision of ELF, AdP and MZ. All authors reviewed the manuscript and approved the final version.

Funding Statement

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design or data collection, and will not be involved in data analysis or preparation of results. AdP holds a salary award (chercheur-boursier) from the FRQ-S.

Declaration of interests

AdP's clinic participates in pharmaceutical clinical trials for HIV antiretrovirals and HCV treatments (ViiV Healthcare, Janssen, Merck, Gilead), received honoraria for consulting on HIV antiretroviral regimen for ViiV Healthcare, and received grants from CIHR and FRQ-S outside the submitted work.

ELF reports grants and personal fees from Merck, grants, personal fees and non-financial support from Roche, and personal fees from GSK, outside the submitted work.

JT is a Merck employee.

FC reports grants from Réseau FRQS-SIDA during the conduct of the study and grants to his institution for HPV-related work but outside of the submitted work from Merk Sharp and Dome, Roche Diagnostics and Becton Dickinson.

MZ, PPT, and CL have nothing relevant to this article to declare.

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APPENDICES
Appendix 1 - Telephone screening questionnaire
Appendix 2 - Pre-eligibility questionnaire
Appendix 3 - Informed consent form
Appendix 4 - Enrolment questionnaire
Appendix 5 - Follow-up questionnaire
Appendix 6 - Protocol for anal swab collection
Appendix 7 - HIV testing

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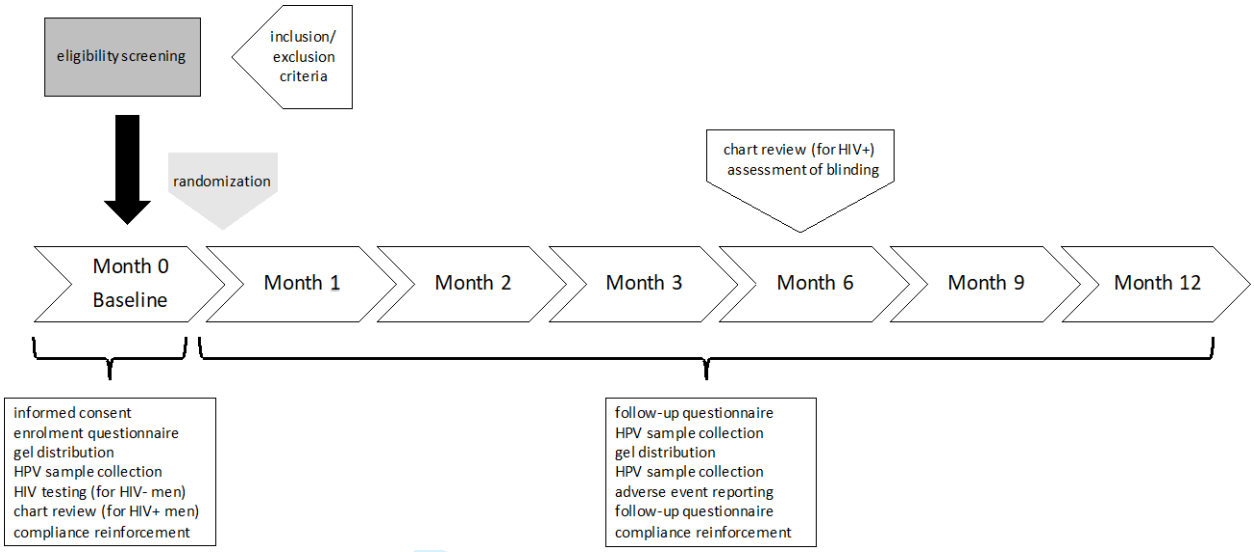

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LIMIT HPV Telephone Screening Questionnaire

Thank you for your interest in our study which aims at evaluating the efficacy of a lubricant gel used during receptive anal intercourse to protect against HPV infection in men having sex with men.

I will now ask you some questions to determine whether or not you are eligible. This will take about 10 minutes. Some of these questions may be of a personal nature. I would like to assure you that all your answers will be kept strictly confidential. Is that OK with you?

[Button] *Verbal consent obtained* [/Button – when pressed record date, show generated LIMIT ID at the top of the page]

1. Are you a man aged over 18 years old?
   [For programming:
   Yes [→ELIGIBLE]
   No [→ NOT ELIGIBLE]

2. For how long do you plan to stay in Montreal?
   Less than a year [→ NOT ELIGIBLE]
   A year or more [→ ELIGIBLE]

3. Are you fluent in either English or French?
   Yes [→ELIGIBLE]*No* [→ NOT ELIGIBLE]

4. How long ago did you last have receptive anal intercourse with a male partner?
   Less than 3 months ago [→ ELIGIBLE]
   3 or more months ago [→ NOT ELIGIBLE]

5. Do you think you will have receptive anal intercourse with a male partner within the next 3 months?
   Yes [→ ELIGIBLE]
   No [→ NOT ELIGIBLE]
   Don't know [→ ELIGIBLE]

6. Based on the past few years, do you expect to have less than 2 or more than 50 DIFFERENT partners in the next year?
   Yes [→ NOT ELIGIBLE]
   No [→ ELIGIBLE]

7. Eligible men must not be receiving treatment for anal or perianal condylomas or anal intraepithelial neoplasia (AIN) during the course of this study. Are you ok with this criterion?
   Yes [→ ELIGIBLE]
   No [→ NOT ELIGIBLE]

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8. Are you currently participating in another study of intervention or treatment of Human Papillomavirus (HPV) or HPV-related disease (condylomas, AIN, anogenital cancer)?
   Yes [→ NOT ELIGIBLE]
   No [→ ELIGIBLE]

9. Do you have any allergies or hypersensitivities to personal lubricants?
   Yes [→ NOT ELIGIBLE]
   No [→ ELIGIBLE]
   Don't know [→ ELIGIBLE]

10. The lubricants that we will use in this study may contain:
    Propylene Glycol
    Glycerin
    Carrageenan
    Aloe barbadensis leaf juice
    Cellulose Gum
    Citric Acid
    Diazolidinyl urea
    Saccharin
    Tetrasodium EDTA

Do you have any known allergies to any of these substances?
Yes [→ NOT ELIGIBLE]
No [→ ELIGIBLE]

[If participant status=INELIGIBLE at this point, DISPLAY SCRIPT 1 and END]
"Thank you for answering my questions. Unfortunately, you are not eligible for our study. We appreciate your interest in our study."

[IF ELIGIBLE, DISPLAY FOLLOWING QUESTIONS]

11. Thank you, I just have a few more questions.

In this study, participants will be given a lubricant gel to use during all receptive anal intercourses during one year, and will be asked to visit the clinic seven times over that year (at 0, 1, 2, 3, 6, 9 and 12 months). At each visit, a short online survey will be completed and a nurse will collect an anal swab. Participants will also keep track of their sexual activities and lubricant use through an online calendar. Do you think you will be able to follow these procedures?
Yes [→ ELIGIBLE]
No [→ NOT ELIGIBLE]

[IF 11=No, participant status=INELIGIBLE, DISPLAY SCRIPT 2 and END]
"Thank you for answering my questions. Unfortunately study participation requires the fulfillment of specific study procedures. Nonetheless, we greatly appreciate your interest in our study."

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12. So far, it looks like you are eligible for this study. Both HIV-positive and HIV-negative men are enrolled in this study. We need to know your HIV-status to see if the effect of the gel differs according to the HIV status, and to plan recruitment at the different study sites. If you never tested positive for HIV previously, we will do an HIV test by pricking your finger to obtain a drop of blood. Please choose the best answer:

    I am HIV positive [→ ELIGIBLE]
    I never tested positive for HIV before, and I am ok with doing an HIV-test for this study. [→ ELIGIBLE]
    I never tested positive for HIV before, but I am NOT ok with doing an HIV-test for this study. [→ NOT ELIGIBLE]

[IF participant status= INELIGIBLE, DISPLAY SCRIPT 2 and END]

Great, thank you for your time. So far you are eligible for the study. We can now plan your enrolment visit.

At this point, record the name, contact information and study ID number to transmit to nurse.

The Research Coordinator could also note in a separate excel sheet on where/how did the caller hear about the study (i.e., poster, Facebook ad, email, friends, etc.).

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LIMIT-HPV Study - Eligibility, Pre-screening questionnaire

(Content template for production of google form)

McGill University has several innovative research projects on Human Papillomavirus (HPV). HPV is the most common sexually transmitted disease (STD) in the world and touches more than 75% of Canadians in their lifetime.

This study investigates whether a lubricant that contains carrageenan is effective in clearing and preventing HPV infection (LIMIT study). Overall, the objective of these studies is to improve the health of ALL sexually active individuals. Results from these studies will be useful to the prevention efforts deployed in Canada as well as elsewhere in the world.

The purpose of the questionnaire below is to assess your eligibility to LIMIT. Thank you for your interest in our studies.

Best regards,

Division of Cancer Epidemiology, McGill University.

* Required

1. How did you heard about us? *

1. *Posters*
2. *Classified ads (Kijiji, AnnonceDonc, LesPacs, Craiglist, etc.)*
3. *Facebook*
4. *Word of mouth (class presentation, friends, familly, collegue)*
5. *Emails (from your department, research assistant, etc.)*

2. What is your gender? *

1. *Man*
2. *Woman*
3. *Other:*

3. What is your age? *

1. *17 years old and under*
2. *Between 18 and 45 years old*
3. *46 years old and over*

4. When was your last sexual intercourse? Here, you must specify with as much accuracy as possible the time elapsed since your last relationship (in week, month or year). *

5. Are you sexually active ? *That is, at least one sexual partner in the last 3 months. *

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1. *Yes*
2. *No*

6. Are you planning to stay in Montreal and its surrounding areas for the next year? *

1. *Yes*
2. *No*
3. *Not sure*

Additional Information

Just a few questions left!

Based on your answer, it may be possible that you're eligible for one of our studies. Please leave us your contact information, we will reach you shortly.

In all cases, we will inform you of the outcome of this questionnaire, whether you are eligible or not.

*Name (and/or nickname) **

*Phone number **

*E-mail address **

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INFORMATION AND CONSENT FORM

Research Project: Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV)

Principal investigators: Dr. Eduardo Franco and Dr. Alexandra de Pokomandy

Institution: Division of Cancer Epidemiology and Family Medicine Department, McGill University

Funding Source: The Canadian Institutes of Health Research (CIHR) and Canadian Cancer Society Research Institute (CCSRI)

You are invited to take part in a clinical trial on human papillomavirus (HPV) infection prevention. Clinical trials include only people who choose to take part. Should you decide to participate in this study, you will be given a copy of this consent form. It provides you with a detailed description of the study, describing all the procedures that will be followed. If you have any questions concerning what is explained here, do not hesitate to ask us. Please take all the time you need to read this form.

INTRODUCTION

HPV is the most common sexually transmitted infection, and most sexually active men will be infected with HPV over their lifetime. Usually these infections go unnoticed or only cause anal or genital warts (condylomas). Although benign, genital warts are difficult to treat and may lead to social embarrassment. Even if most HPV infections are temporary and will be cleared naturally, certain types cause more persistent infections that can progress to cancer.

Researchers identified that *carrageenan*, an inexpensive gelling agent that is already commonly used in food and cosmetics, is able to interfere with HPV infection. This study will examine if a personal sex lubricant containing carrageenan, directly applied to the skin and used during sexual activities, can decrease HPV infection. Such an inexpensive intervention would help reduce the burden of genital warts, and HPV-associated cancers in a cost-effective way. The gel being studied is already commercialized and sold as a personal lubricant.

PURPOSE OF THE STUDY

This study will investigate whether or not a lubricant gel that contains carrageenan is effective in preventing anal HPV infection in men who have sex with men. We will recruit 380 adult men participants in Montreal, including 110 HIV-seropositive men.

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STUDY PROCEDURE

Duration and number of visits

Your participation in this study will be for 12 months and will include 7 visits.

Table of study visits and procedures

	Visit 1 (Enrollment)	Visit 2 (1 mo)	Visit 3 (2 mo)	Visit 4 (3 mo)	Visit 5 (6 mo)	Visit 6 (9 mo)	Visit 7 (12 mo)
Questionnaire	x	x	x	x	x	x	x
Anal HPV test	x	x	x	x	x	x	x
HIV test*	x						x
Estimated duration	60 min	30 min	30 min	30 min	30 min	30 min	30 min

* For participants not known to be seropositive for HIV.

Randomization

If you are eligible and consent to enroll in this study, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor the study staff can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in Group 1 you will receive a personal lubricant that contains carrageenan.

If you are in Group 2 you will receive a personal lubricant that does not contain carrageenan.

Neither you nor the study staff will know if you are getting the carrageenan gel or the comparison gel. The reason for this is that if men know which gel they are using, it may affect what they think and say about it. If the study staff is aware of participants' group assignment, it may affect how they interpret what they see and hear in the exams and interviews. Only after the study is over will the researchers be able to find out the intervention that each participant was assigned, and whether or not the study results show a difference between the 2 groups. If you want to know which gel you were using, you will be able to find out when the whole study is finished.

Clinic Visits

You will be asked to visit the research nurse 7 times for the collection of anal specimens for HPV testing over the 12 months of your participation. At your first visit, a research nurse will provide you with instructions on how and when to apply the study gel. The nurse will collect your first anal HPV specimen in a private room at the clinic, by inserting and rotating a cotton-tip swab in your anus. This procedure is not painful, and only takes few seconds. In addition, you will be asked to complete an electronic survey. This first survey will ask questions about your background, medical and sexual history, condom and lubricant usage, smoking habits and alcohol consumption. The research nurse or coordinator will be available at all times should you need help. Before leaving, you will be provided with a one-month supply of gel. This first visit will last about one hour.

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You will visit the clinic at 1 month, 2 months, 3 months, 6 months, 9 months and 12 months after your first visit. You will be asked to abstain from receptive anal sex and gel use for at least 48 hours prior to each visit. At the clinic, the nurse will collect an anal specimen for HPV testing in a private room, and you will be asked to complete a follow-up survey about your recent sexual activities, use of study gel, and medical history. Each survey will take about 15 minutes to complete. At your one- and two-month visit, the research nurse will provide you with a one-month supply of study gel. At every visit thereafter (except for your final visit), the research nurse will provide you with 3 months' supply of gel, i.e., enough to last you until the next visit. Each visit will last about 30 minutes.

You will be asked to continue using the assigned intervention for the complete follow-up period (12 months), along with condom use for prevention of other sexually transmitted infections.

Online calendars

You will be given an access code with which you can log on to a secure internet website to complete confidential electronic calendars. You will be asked to track your sexual activities and study gel use on a weekly basis using the online calendar. The calendars will take approximately 5 minutes per week to update. Help will be available through email and telephone should you need assistance.

Laboratory testing of anal specimens

The anal specimens collected for HPV testing will be sent to the laboratory and will be tested for 36 strains of HPV, including the most common types of HPV that can cause anal cancer. HPV testing is only done for research purposes and it is not used in standard clinical care of men. Therefore, we are not planning to reveal individual test results unless specifically requested. In such a case, we can send them to your doctor at the end of your study participation. It is important to know that an HPV infection can last for a very long time. Thus, a positive test for an HPV infection does not mean that it was recently acquired.

We also ask you for permission to store the samples for future studies on HPV infection using more sophisticated techniques not yet available.

HIV status

- **If you have never been diagnosed HIV-seropositive:**
  For participants who never tested seropositive for HIV, the nurse will conduct a rapid HIV test with a drop of your blood obtained through a finger prick. We will test you at enrolment and at study exit. This will serve to verify the HIV status of participants. Please note that if your rapid test gives a HIV-seropositive result, we will need to confirm this finding with a second test using a regular blood sample and more accurate laboratory equipment. We will then ask you to abstain from sexual activities or to use protection when engaging in sex until this result can be confirmed. The nurse will immediately refer you to a physician for follow-up. If you are found to be HIV-positive at study entry (not at study exit), then the following paragraph will apply to you as well.

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- **If you are living with HIV:**
  For participants living with HIV, a review of your medical chart (at your usual HIV clinic) will be done to collect data about your HIV medical history and HIV lab results (CD4 counts, HIV viral load). We will therefore ask you to provide us with the contact information of your HIV physician.

End of study participation
Your participation in the study will be stopped early if you consider it to be in your best interest or for personal reasons, or if a physician considers it to be in your best interest because of safety reasons or your well-being.

BENEFITS
You should not expect any direct health benefits from participating in this study. While researchers hope that the intervention under study will be useful in protecting against infection with HPV, **there is no proof of this yet**. The information from this study will help researchers learn more about carrageenan as a potential treatment and preventative against anal HPV infection and anal cancer.

RISKS
Using either carrageenan or the comparison gel may cause itching, burning or pain, but these symptoms are unlikely (<5% chance). If you experience any side effects, discontinue use of the gel and contact the study nurse. Since the study gel (with or without carrageenan) does not prevent other sexually transmitted infections, you will be asked to continue using condoms for the duration of the trial.

The collection of an anal specimen for HPV testing is a safe procedure. There is a possibility of slight discomfort during the insertion of the cotton-tip swab to collect the specimen.

For the HIV-negative participants, there may be small amount of pain during the finger prick for the HIV tests. There may be psychological distress associated with testing positive for HIV. In the event that you test positive, you will receive counseling and referral for standard care.

If you experience any adverse events during your involvement in the study, you will be referred to the McGill University Student Health Services Clinic located at 3600 McTavish Street West or the MUHC Chronic Viral Illnesses Service clinic located on the 2nd floor of the MUHC Glen site 1001 Décarie.

CONFIDENTIALITY
The results from the laboratory testing of your specimens and the responses you give in the surveys will be treated with strict confidentiality. All the information that you provide online will be stored in a secure server. Only researchers who are part of the study will have access to the data. No names or other information that could identify yourself as a participant will be released. All the data from this study will be analyzed as groups without linkage of names to any data.

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The actual specimens will not be made available to investigators that are not involved with this study, nor will they be sold for commercial use. They will only be used for the purposes outlined in this consent form. They will be securely stored at University of Montreal (laboratory of co-investigator, Dr. Francois Coutlée) for as long as they are needed for the verification of laboratory results, testing with additional methods, and for research audit purposes. Your name will not be linked to any specimen.

Health Canada and the McGill University Faculty of Medicine Institutional Review Board may review the study data and files to ensure sound management of this study. For this reason, the records derived from the trial will be kept for 25 years. These records will be destroyed after 25 years.

YOUR RIGHTS

Your participation in this study is completely voluntary. You are free to withdraw from the study at any time. Your decision to withdraw will have no effect on your current or future health care. As a participant, you will be informed of any new information that may affect your willingness to participate in the trial.

By accepting to participate in this research project, you are not waiving any of your legal rights nor discharging the researchers, the sponsor or the institution, of their civil and professional responsibility.

COST

There are no costs to you, direct or indirect.

COMPENSATION

You will receive between $40 and $50 per completed study visit in compensation for costs (transport, parking, food) and/or loss of income incurred from your participation in this study. The maximum total compensation for this study (7 study visits) is $300.

ADDITIONAL INFORMATION

If at any time during your study participation you have questions about HPV or this study, you may contact one of our research staff Mrs. Natalia Morykon, at 514-398-3710 or Mrs. Karène Proulx-Boucher at 514-934-1934 extension 32146. You may also contact Dr. Mariam El-Zein, Associate Director for Research at the Division of Cancer Epidemiology, at 514-398-1489 or mariam.elzein@mcgill.ca.

If you have questions regarding your rights as a research participant, please contact Ms. Ilde Lepore, Senior Ethics Administrator of the Institutional Review Board, Faculty of Medicine at 514-398-8302 or ilde.lepore@mcgill.ca.

ETHICS APPROVAL

Health Canada has authorized the use of carrageenan for this investigational study. The McGill Institutional Review Board has reviewed this study for ethical acceptability.

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Research Project: Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV)

I. Participant's consent

I have read this consent form. I have been informed of the purpose of this study. I am aware of the study procedures and the risks and benefits of my participation. I have been informed that my participation in this study is voluntary, and that I can withdraw from this study at any time without giving a reason. I consent to take part in this study. I do not give up any of my legal rights by signing this consent form.

A dated and signed copy of the present information and consent form was given to me.

_____

Name of participant

_____ _____

Signature of participant Date

II. Signature of the person who obtained consent

I have explained the terms of the present information and consent form to the research participant and I answered all his questions.

_____

Name of person obtaining consent

_____ _____

Signature of person obtaining consent Date

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LIMIT-HPV Study - Enrolment Questionnaire
(Content template for production of computerized instrument)

IMPORTANT INFORMATION

Questions and instructions appear in regular text
Responses appear in *italicized text*
Notes and skip patterns for programming appear in [square brackets]

Questions that must be answered are marked [*REQUIRED]
All other questions are optional

For multiple choice questions, the number or letter that appears before each response option indicates the coding or numbering for the response, the number/letter is for programming purposes only and is not to appear in the participant questionnaire
Codes: 99 – skipped by the skip pattern or not applicable; 88 – left blank by the participant; 77 – don't remember/don't know

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Introduction

Thank you for being part of the study! Your participation helps us answer questions about the potential effectiveness of a Carrageenan-containing gel in reducing Human Papillomavirus (HPV) transmission.

This 30-minute survey will ask questions about you, your health and sexual history, and recent sexual behaviours. We understand that some of these questions may be sensitive and of a personal nature. We assure you that all your answers will be kept completely confidential.

There is no right or wrong answer to any question. Some questions ask you to think back over your adult years, or over the past several months, to recall specific information. Please take your time to consider each question carefully. We would greatly appreciate your efforts to answer all questions as best as you can. It is crucial for a research study to have complete and accurate information and we need your help in making this study successful.

Most questions require that you simply click on the response that applies to you. Other questions ask you to enter a specific answer, such as a number, a date, or a short text. Depending on your answer for some questions, you may be skipped past some questions. This is to save you time so that you won't have to answer questions that do not apply to you.

Ready to start? Press continue!

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General information

This part of the questionnaire concerns general information about you and where you live.

1. What is your date of birth?
   [Date field: dd/mm/yyyy - *REQUIRED]

2. In what country were you born?
   [Selection field]

[IF 2=Canada] 2.1 In which province were you born?
   [Selection field]

3. The Montreal area is made up of many ethnic groups. We would like to know in which group you would place yourself. Please indicate the most appropriate category.
   1. *French Canadian*
   2. *English Canadian*
   3. *Black Canadian*
   4. *Aboriginal*
   5. *American*
   6. *Latin American*
   7. *Haitian*
   8. *European*
   9. *African*
   10. *South Asian*
   11. *East Asian*
   12. *Middle Eastern*
   13. *Other, please specify:* [text field 3.1]

4. What is the highest degree of education that you have completed?
   1. *Less than elementary*
   2. *Elementary*
   3. *Secondary (High school)*
   4. *College or CEGEP*
   5. *University*

4.1 What is your current work or life situation?
   1: Working full time (30 hours/week or more)
   2: Working part time (<30 hours/week)
   3: On parental leave
   4: On temporary sick leave
   5: Looking for work
   6: No longer able to work
   7: No longer wish to work
   8: Other, please specify: [text field 4.1.1]

5. How long have you lived in Montreal?
   [#field] [options field 5.1- choose unit - 1: months; 2: years] *months OR years*

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Smoking History

The following questions are about your tobacco smoking habits. Please try to be as specific as possible in your answers.

6. Have you ever smoked cigarettes regularly – that is, one cigarette or more each day for a year or more?
   1: Yes
   0: No

[IF 6=No, SKIP to 10]

7. At what age did you start to smoke regularly?
   Age in years: [# field]

8. Do you still smoke regularly?
   1: Yes
   0: No

[IF 8=No] 8.1 At what age did you last stop smoking regularly?
   Age in years: [# field]

9. During your smoking years, how many cigarettes, on average, did you smoke per day?
   Cigarettes per day: [# field]

Alcohol and Drug Consumption

The next few questions are about your alcohol consumption during the **past year**. A drink refers to 1 can/bottle (375 mL) of beer, 1 glass of wine, 1 can or bottle of wine cooler, 1 cocktail, or 1 shot of liquor.

10. During the **past year**, on average, how many days per week or days per month did you have at least one drink of any alcoholic beverage?
    [#field] [options field 10.1- choose unit: per week, per month] *per week OR per month*
    0: Did not drink

[IF 10=Did not drink, SKIP to 13]

11. On the days when you drank in the **past year**, about how many drinks did you drink on average?
    Average number of drinks per drinking day: [# field]

12. Considering all types of alcoholic beverages, how many times in an average month over the **past year** did you have 5 or more drinks on an occasion?
    Times per month: [# field]
13. Have you **ever** injected yourself with substances or drugs?
    1: Yes
    0: No

[If 13 =Yes, answer 13.1 and 13.2]

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13.1 When was the **FIRST** time you ever used injection drugs (approximately)?
[date field mm/yyyy]
77: Don't remember

13.2 When was the **LAST** time you used injection drugs (approximately)?
[date field mm/yyyy]
77: Don't remember

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Lifetime Sexual History

The next questions are about your sexual history. We realize that this is a personal subject, but it is very important to the study of Human Papillomavirus (HPV). Please take the time to recall this information as accurately as possible. Some questions in this section refer to your sexual experience over your lifetime, whereas others refer only to recent experience. Please remember that all the information you give will be kept entirely confidential.

Throughout this survey, we will refer to various specific sexual acts. These terms are explained below so that everyone attaches the same meanings to them. Note that female genitals were kept in the definitions to account for sexual activities participants may have or have had with women too. Please be sure to read these definitions. If you need any further help or explanation, please ask the Research Nurse.

Oral sex:	A person's mouth on a sex partner's genital area (penis, vulva or vagina, but NOT the anus which we will refer to as rimming).
Rimming:	A person's tongue around the anus rim or in the anal canal (for this questionnaire, it includes any type of contact between a tongue and an anus).
Anal sex:	A man's penis in a sex partner's anus or rectum.
Receptive anal sex:	Being penetrated by the penis of your sex partner(s) during anal sex (being bottom).
Mutual masturbation:	Hand stimulation of a person's anal or genital area by his/her partner, NOT involving penetration of the penis in the mouth, vagina or anus.
Fisting:	Penetration of the hand (fist) in a partner's anus or rectum.
Sexual activity:	Mutual masturbation, oral sex, vaginal sex, or anal sex.
Sex partner(s):	People who have engaged in sexual activities together – whether once, or just a few times, or as regular partners, or as married partners.

14. Please think about all the people with whom you have engaged in sexual activity. In total, with how many people have you engaged in any sexual activity in your **lifetime**?
    [# field 14]
    How many were male (i.e. possessing male genitals)?
    [# field 14.1]
    How many were female (i.e. possessing female genitals)?
    [# field 14.2]

15. How old were you when you had your **first** sexual activity with a person of same sex?
    [Selection field]
16. Since you first started having sexual activities with men, with how many different men per year, on average, would you say you had sexual activities with?
    1. *None*
    2. *One per year*

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3. *2 – 5 per year*
4. *6 – 9 per year*
5. *10 – 14 per year*
6. *15 – 24 per year*
7. *25 – 49 per year*
8. *50 – 100 per year*
9. *More than 100 per year*

17. In the **last year only**, how many different male sex partners have you had?
    1. *None*
    2. *One per year*
    3. *2 – 5 per year*
    4. *6 – 9 per year*
    5. *10 – 14 per year*
    6. *15 – 24 per year*
    7. *25 – 49 per year*
    8. *50 – 100 per year*
    9. *More than 100 per year*

18. In the last **month**, have you had one or more **new** male sex partner(s)?
    1: Yes
    0: *No*

19. Do you currently have a stable male sex partner (i.e. someone with whom you have sexual activities with on a regular basis, but not necessarily an exclusive partner)?
    1: Yes
    0: *No*

[IF 19=No, SKIP to 22]

20. Do you only have anal sex with your stable male sex partner?
    1: Yes
    0: *No*

21. Does your stable male sex partner have sex with other men?
    1: Yes, or I think so
    0: *No, or I don't think so*
    77: Don't know

22. Did you ever receive fisting in your anus (i.e. penetration of your sex partner's fist in your rectum)?
    1: Yes, or I think so
    0: *No, or I don't think so*
    77: Don't know

[IF 22=Yes] 22.1 How many times in your lifetime, did you receive fisting?
[# field 14]

For the next questions, we only refer to the times you engaged in receptive anal sex.

23. Have you ever had receptive anal sex, i.e. the penis of your sex partner penetrates your anus?

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1: Yes
0: *No*

[IF 23=No, SKIP to 27]

24. In the **last year only**, how many men have you had receptive anal sex with?
    1. *None*
    2. *One per year*
    3. *2 – 5 per year*
    4. *6 – 9 per year*
    5. *10 – 14 per year*
    6. *15 – 24 per year*
    7. *25 – 49 per year*
    8. *50 – 100 per year*
    9. *More than 100 per year*

25. In the **last year only**, how often did your sex partner(s) wear a condom (rubber) when you had receptive anal sex?
    0: Never (0%)
    1: Rarely (1-24%)
    2: Occasionally (25-49%)
    3: Often (50-74%)
    4: Almost always (75-99%)
    5: Always (100%)

26. Have you ever experienced bleeding from your anus following receptive anal sex?
    1: Yes
    0: *No*

Sexual Activities in the Past Month

The next questions are about sexual activities during the past month, that is, **between dd/mm/yyyy** [CALCULATE TODAY's DATE-30] **and today**.

27. During that period, did you engage in sexual activity with one or more partner(s)?
    1: Yes
    0: No

[IF 27=No, SKIP to 47]

28. How many sex partners did you have in the **past month**?
    [# field 28]
    How many were male (i.e. possessing male genitals)?
    [# field 28.1]
    How many were female (i.e. possessing female genitals)?
    [# field 28.2]

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29. Considering all your sex partners in the **past month**, how many times in total did you engage in sexual activities? By sexual activity, we mean any of mutual masturbation, oral, vaginal, anal sex, rimming or fisting.
    [#field] [options field 29.1- choose unit – 1: per week; 2: in total] *per week OR in total*

30. In the **past month**, how many times in total did you engage in the following specific sexual activities?
    30.1 receiving oral anal (rimming), i.e. any contact between the tongue of your sex partner and your anus?
    [#field] [options field 30.1- choose unit – 1: per week; 2: in total] *per week OR in total*

    30.2 receiving fingers of your sex partner in your anus?
    [#field] [options field 30.2- choose unit – 1: per week; 2: in total] *per week OR in total*

    30.3 receiving an object (dildo/vibrator or other) in your anus or rectum (by your partner or yourself)?
    [#field] [options field 30.3- choose unit – 1: per week; 2: in total] *per week OR in total*

    30.4 receiving fisting (i.e. the fist of your partner in your anus or rectum?
    [#field] [options field 30.4- choose unit – 1: per week; 2: in total] *per week OR in total*

For the next questions, we only refer to the times you engaged in <u>receptive</u> anal sex.

31. With how many male partners did you engage in <u>receptive</u> anal sex in the **past month**?
    [#field]

32. How many times did you have <u>receptive</u> anal sex in the **past month**?
    [#field] [options field 32- choose unit – 1: per week; 2: in total] *per week OR in total*

33. When was the last time you had <u>receptive</u> anal sex?
    [date field dd/mm/yyyy]
    77: Don't remember

34. How often did you use condoms during <u>receptive</u> anal sex in the **past month**?
    0: Never (0%)
    1: Rarely (1-24%)
    2: Occasionally (25-49%)
    3: Often (50-74%)
    4: Almost always (75-99%)
    5: Always (100%)

[IF 34=Never, SKIP to 38]

When you used condoms for <u>receptive</u> anal sex (i.e. you were bottom) in the **past month**…

35. Did the condom **ever** break or slip off?
    1: Yes
    0: No
    77: Don't remember

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36. Did your partner **always** put the condom on before starting to penetrate you?
    1: Yes
    0: No
    77: Don't remember

37. Did your partner **ever** take the condom off then continued to penetrate you without the condom?
    1: Yes
    0: No
    77: Don't remember

Personal lubricants are liquids used during sexual activities to reduce friction between body parts or between body parts and other objects. We do not include saliva as a lubricant here.

38. How often did you use a lubricant when you were receiving receptive anal sex in the **past month**?
    0: Never (0%)
    1: Rarely (1-24%)
    2: Occasionally (25-49%)
    3: Often (50-74%)
    4: Almost always (75-99%)
    5: Always (100%)

39. How often did you use a lubricant during other receptive anal sexual activities in the **past month** (i.e. while you were receiving object or fisting in your anus or rectum)?
    0: Never (0%)
    1: Rarely (1-24%)
    2: Occasionally (25-49%)
    3: Often (50-74%)
    4: Almost always (75-99%)
    5: Always (100%)

[IF 38 and 39=Never/SKIPPED, SKIP to 43]

When you used lubricants in the **past month**…

40. Where did you or your partner apply the lubricant? (Mark all that apply)
    1. *Around own anus*
    2. *Inside own rectum*
    3. *On partner's penis*
    4. *Outside of the condom*
    5. *Inside of the condom*
    6. *Around partner's anus*
    7. *Inside partner's rectum*
    8. *On a sex toy that was placed on your genitals or inside your anus*
    9. *Elsewhere (please specify):* [text fields up to 3: 40.1-40.3]

41. How many teaspoons (approximate average) were used per sexual activity in the **past month**?
    1. *Greater than or equal to 1, but less than 2*
    2. *Greater than or equal to 2, but less than 3*
    3. *Greater than or equal to 3, but less than 4*

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4. *Greater than or equal to 4, but less than 5*
5. *Greater than 5*

42. What specific brand(s) of gel lubricant(s) did you use in the **past month**? (Mark all that apply)
    a: Astroglide
    b: Bioglide
    c: ID
    d: JO
    e: K-Y
    f: Liquid Silk
    g: Maximus
    h: OMY
    i: Pink
    j: PJUR
    k: Slippery Stuff
    l: Sylk
    m: Uberlube
    n: WET
    o: *Other (please specify):* [text fields up to 3: 42.1-42.3]

Sexual Activities in the Past Week

The next questions are about sexual activities during the past 7 days, that is, **between dd/mm/yyyy** [CALCULATE TODAY's DATE-7] **and today**.

43. How many times did you have receptive anal sex with a man in the **past 7 days**?
    [Drop down selection menu: numbers 0-20]

44. How many times did you use condoms during receptive anal sex in the **past 7 days**?
    [Drop down selection menu: numbers 0-20]

45. How many times did you use personal lubricants during receptive anal sex in the **past 7 days**?
    [Drop down selection menu: numbers 0-20]

46. How many times in total did you engage in the following specific sexual activities in the **past 7 days**?
    46.1 receiving oral-anal (rimming), i.e. any contact between the tongue of your sex partner and your anus?
    [Drop down selection menu: numbers 0-20]

    46.2 receiving fingers of your sex partner in your anus?
    [Drop down selection menu: numbers 0-20]

    46.3 receiving an object (dildo/vibrator or other) in your anus or rectum (by your partner or yourself)?
    [Drop down selection menu: numbers 0-20]

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46.4 receiving fisting (i.e. the fist of your partner in your anus or rectum?
[Drop down selection menu: numbers 0-20]

Medical History

The next questions ask about medical conditions or health problems you may have currently or had in the past.

47. Has a doctor **ever** told you that you were HIV-positive?
1: Yes
0: No

48. Has a doctor **ever** diagnosed you with any chronic health conditions (other than HIV)?
1: Yes
0: No

[If 48=Yes] 48.1 What chronic health conditions have you been diagnosed with (excluding HIV)?
[textbox 48.1]

49. Do you currently take any medications prescribed by a doctor [this includes medication you may take against HIV if the case]?
1: Yes
0: No

[If 49=Yes] 49.1 Please list all the medications prescribed by a doctor that you currently take
[textbox 48.1]

50. Do you have, or have you had, any allergies?
1: Yes
0: No

[If 50=Yes] 50.1 What are/were you allergic to?
[textbox 50.1]

51. Have you **ever** had surgery?
1: Yes
0: No

[If 51=Yes] 51.1 Which surgeries did you have?
[textbox 51.1]

52. Have you **ever** been hospitalized?
1: Yes
0: No

[If 52=Yes] 52.1 What were the reasons for your hospitalization(s)?
[textbox 52.1]

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53. Have you **ever** been vaccinated against HPV (i.e. with Gardasil or Cervarix)?

1: Yes
0: No

[IF 53=Yes, answer 53.1 and 53.2]

53.1 Which HPV vaccine did you receive?

1: Gardasil
2: Cervarix
3: Gardasil 9
77: Don't know or don't remember

53.2 How many vaccine doses did you receive?

[Drop down selection menu: numbers 1-3 or simple choice between 1, 2 or 3]
77: Don't know or don't remember

53.3 When was your first HPV shot?

[Date field: dd/mm/yyyy, and an open field]

54. Did a doctor **ever** tell you that you had one of the following conditions or sexually transmitted infections (STIs)?

Condition	*1:**Yes***	If yes, check if it was within the **last 6 months** [only available if yes, *0/1*]	*0: **No***	*77: **Don't know***
a) Venereal warts or condylomas				
b) Chlamydia				
c) Lymphogranuloma Venereum (LGV)				
d) Anal or genital herpes				
e) Syphilis				
f) Gonorrhea				
g) Ulcers or genital sores				
h) Hepatitis B				
i) Hepatitis C				
j) Anal high grade dysplasia OR anal intraepithelial neoplasia grade 2 or 3 (AIN 2 or 3) OR anal precancer				
k) Anal cancer				

55. In the **last five years only**, have you ever experienced pain in the anus caused by hemorrhoids?

0. Never
1. Rarely
2. Sometimes
3. Frequently

56. In the **last five years only**, have you ever had a discharge, other than blood, from your anus?

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0. *Never*
1. *Rarely*
2. *Sometimes*
3. *Frequently*

57. Have you ever had sex with a partner whom you know had condyloma or genital warts?
1: Yes
0: No

Thank you very much for your participation!

All the information you have provided will be kept strictly confidential.

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LIMIT-HPV Study – Follow-up Questionnaire
(Content template for production of computerized instrument)

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IMPORTANT INFORMATION

Questions and instructions appear in regular text
Responses appear in *italicized text*
Notes and skip patterns for programming appear in [square brackets]

Questions that must be answered are marked [*REQUIRED]
All other questions are optional

For multiple choice questions, the number or letter that appears before each response option indicates the coding or numbering for the response, the number/letter is for programming purposes only and is not to appear in the participant questionnaire
Codes: 99 – skipped by the skip pattern or not applicable; 88 – left blank by the participant; 77 – don't remember/don't know

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Introduction

Thank you for returning to complete your follow-up questionnaire! We appreciate your continued participation.

This 20 minute survey will be asking you to update your personal and medical information, as well as your recent sexual behaviour. Please take your time to consider each question carefully. A good guess is always better than no information at all. You can leave blank any questions that you feel uncomfortable answering or do not know the answer to. We would greatly appreciate your efforts to answer all questions as best as you can.

We will also ask you about your experience with the study lubricant. Remember that you are not being evaluated on your use of the study lubricant, so please answer all questions as honestly as possible. The accuracy of this information is valuable to us.

Ready? Press continue to begin!

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Sexual Behaviour Update

The next questions are about sexual behaviour you may have engaged in since your last survey on **dd/mm/yyyy** [LAST QUESTIONNAIRE DATE].

We realize this is a personal subject, but it is very important to the study of Human papillomavirus (HPV). Please take the time to recall this information as accurately as possible. Please remember that all the information you give will be kept entirely confidential.

Throughout this survey, we will refer to various specific sexual acts. These terms are explained below so that everyone attaches the same meanings to them. Note that female genitals were kept in the definitions to account for sexual activities participants may have or have had with women too. Please be sure to read these definitions. If you need any further help or explanation, please ask the Research Nurse.

Oral sex:	A person's mouth on a sex partner's anal or genital area (penis, vulva or vagina, but NOT the anus which we will refer to as rimming).
Rimming:	A person's tongue around the anus rim or in the anal canal (for this questionnaire, it includes any type of contact between a tongue and an anus).
Anal sex:	A man's penis in a sex partner's anus or rectum.
Receptive anal sex:	Being penetrated by the penis of your sex partner(s) during anal sex (being bottom).
Mutual masturbation:	Hand stimulation of a person's anal or genital area by his/her partner, NOT involving penetration of the penis in the mouth, vagina or anus.
Fisting	Penetration of the hand (fist) in a partner's anus or rectum.
Sexual activity:	Mutual masturbation, oral sex, vaginal sex, or anal sex.
Sex partner(s):	People who have engaged in sexual activities together – whether once, or just a few times, or as regular partners, or as married partners.

1. Since your **last** survey, did you engage in sexual activity with one or more partner(s)?
   1: Yes
   0: No

[IF 1=No, SKIP to 24]

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2. How many sex partners did you have since your **last** survey?
   [# field 2]
   How many were male (i.e. possessing male genitals)?
   [# field 2.1]
   How many were female (i.e. possessing female genitals)?
   [# field 2.2]

3. Since your **last** visit, how many different male sex partners have you had?
   1. *None*
   2. *One*
   3. *2 – 5*
   4. *6 – 9*
   5. *10 – 14*
   6. *15 – 25*
   7. *More than 25*

4. Since your **last** visit, did you have at least one **new** male sex partner?
   1: Yes
   0: *No*

5. Since your **last** visit, have you had receptive anal sex (i.e. you were bottom)?
   1: Yes
   0: *No*

[IF 5=No, SKIP to 11]

6. Since your last visit, during receptive anal sex did your partner wear a condom (rubber)?
   0: Never (0%)
   1: Rarely (1-24%)
   2: Occasionally (25-49%)
   3: Often (50-74%)
   4: Almost always (75-99%)
   5: Always (100%)

[IF 6=Never, SKIP to 10]

When you used condoms for receptive anal sex **since your last survey** …

7. Did the condom **ever** break or slip off?
   1: Yes
   0: No
   77: Don't remember

8. Did your partner **always** put the condom on before starting to penetrate you?
   1: Yes
   0: No

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77: Don't remember

9. Did your partner **ever** take the condom off then continue to penetrate you without the condom?
   1: Yes
   0: No
   77: Don't remember

10. Since your **last** visit**,** have you ever experienced bleeding from your anus following receptive anal sex?
   1: Yes
   0: *No*

11. Since your **last** visit, how many times in total did you engage in the following specific sexual activities?
   11.1 receiving oral anal (rimming), i.e. any contact between the tongue of your sex partner and your anus? [#field] [options field 11.1- choose unit – 1: per week; 2: in total] *per week* OR *in total*

   11.2 receiving fingers of your sex partner in your anus?
   [#field] [options field 11.2- choose unit – 1: per week; 2: in total] *per week* OR *in total*

   11.3 receiving an object (dildo/vibrator or other) in your anus or rectum (by your partner or yourself)? [#field] [options field 11.3- choose unit – 1: per week; 2: in total] *per week* OR *in total*

   11.4 receiving fisting (i.e. the fist of your partner in your anus or rectum?
   [#field] [options field 11.4- choose unit – 1: per week; 2: in total] *per week* OR *in total*

The Study Gel

12. Since your **last** visit, have you used the study gel during sexual activities?
   1: Yes
   2: No

[IF 12=No, SKIP to 19]

13. Since your **last** visit, where did you or your partner apply the study gel during sexual activities OTHER than receptive anal sex? (Mark all that apply)
   1. *Around own anus*
   2. *Inside own rectum*
   3. *On partner's penis*
   4. *Outside of the condom*
   5. *Inside of the condom*
   6. *Around partner's anus*

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7. *Inside partner's rectum*
8. *On a sex toy that was placed on your genitals or inside your anus*
9. *Elsewhere (please specify):* [text fields up to 3: 13.1-13.3]

14. Since your **last** visit, have you used the study gel during receptive anal sex?
    1: Yes
    0: No

[IF 14=No, SKIP to 18]

15. When was the last time you used the study gel during receptive anal sex?
    [date field dd/mm/yyyy]
    77: Don't remember

16. During receptive anal sex, how did you or your partner apply the study gel? (Mark all that apply)
    1. *Around own anus*
    2. *Inside own rectum*
    3. *On partner's penis*
    4. *Outside of the condom*
    5. *Inside of the condom*
    6. *Around partner's anus*
    7. *Inside partner's rectum*
    8. *On a sex toy that was placed on your genitals or inside your anus*
    9. *Elsewhere (please specify):* [text fields up to 3: 16.1-16.3]

17. How many teaspoons (approximate average) were used per round of receptive anal sex since your **last** survey?
    0: Greater than or equal to 1, but less than 2
    1: Greater than or equal to 2, but less than 3
    2: Greater than or equal to 3, but less than 4
    3: Greater than or equal to 4, but less than 5
    4: Greater than 5

18. Was there anything that made it difficult for you to use (or not to use) the study gel during receptive anal sex? (Mark all that apply)
    a: Application of the study gel is too difficult
    b: The packaging is too inconvenient
    c: You did not have the study gel on you at the time of intercourse
    d: You forgot to use the study gel
    e: You did not want to use lubricants
    f: You preferred other brands to the study gel
    g: You think that the quality of the study gel is poor (e.g., odour, feel, etc.)
    h: Use of the gel caused discomfort/adverse reactions to you (please inform the nurse)
    i: Partner(s) does/did not want to use lubricants
    j: Partner(s) is/are allergic to ingredients of the study gel
    k: Partner(s) preferred other brands to the study gel

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l: Partner(s) think(s) that the quality of the study gel is poor (e.g., odour, feel, etc.)
m: Use of the gel caused discomfort/adverse reactions to your partner(s) (please inform the nurse)
n: Other: [text fields, up to 3: 18.1-18.3]
o: Nothing, it was easy to use

19. Since your **last** survey, did you use any lubricants other than the study gel?
1: Yes
0: No

[IF 19=Yes] 19.1 What other brand(s) of gel lubricant(s) did you use **since your last survey**?
a: Astroglide
b: Bioglide
c: ID
d: JO
e: K-Y
f: Liquid Silk
g: Maximus
h: OMY
i: Pink
j: PJUR
k: Slippery Stuff
l: Sylk
m: Uberlube
n: WET
o: *Other (please specify):* [text fields up to 3: 19.1-19.3]

Sexual Activities in the Past Week

The next questions are about sexual activities during the past 7 days, that is, **between dd/mm/yyyy** [CALCULATE TODAY's DATE-7] **and today**.

20. How many times did you have receptive anal sex in the **past 7 days**?
[Drop down selection menu: numbers 0-20]

21. How many times did you use condoms during receptive anal sex in the **past 7 days**?
[Drop down selection menu: numbers 0-20]

22. How many times did you use the study gel during receptive anal sex in the **past 7 days**?
[Drop down selection menu: numbers 0-20]

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23. In the **past 7 days**, how many times in total did you engage in the following specific sexual activities?

23.1 receiving oral-anal (rimming), i.e. any contact between the tongue of your sex partner and your anus? [Drop down selection menu: numbers 0-20]

23.2 receiving fingers of your sex partner in your anus?
[Drop down selection menu: numbers 0-20]

23.3 receiving an object (dildo/vibrator or other) in your anus or rectum (by your partner or yourself)? [Drop down selection menu: numbers 0-20]

23.4 receiving fisting (i.e. the fist of your partner in your anus or rectum?
[Drop down selection menu: numbers 0-20]

Medical Update

The next questions refer to your medical history **since your last survey on dd/mm/yyyy** [LAST QUESTIONNAIRE DATE].

24. Have you received any vaccine shot against HPV (i.e. with Gardasil or Cervarix)?

1: Yes
0: No

[IF 24=Yes] 24.1 Which HPV vaccine did you receive?

1: *Gardasil*
2: Cervarix
3: Gardasil 9
77: Don't know or don't remember

24.2 How many vaccine doses did you receive?
[Drop down selection menu: numbers 1-3 or simple choice between 1, 2 or 3]
77: Don't know or don't remember

24.3 When was your first HPV shot?
[Date field: dd/mm/yyyy, and an open field]

25. Since your **last** survey, did a doctor tell you that you had one of the following conditions/sexually transmitted infections (STIs)?

Condition	*1: **Yes***	*0: **No***	*77: **Don't Know***
a) Venereal warts, condylomas, or papilloma virus infection			
b) Chlamydia			

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c) Lymphogranuloma Venereum (LGV)			
d) Genital Herpes			
e) Syphilis			
f) Gonorrhoea			
g) Ulcers of genital sores			
h) Hepatitis B			
i) Hepatitis C			
j) Anal high grade dysplasia OR anal intraepithelial neoplasia grade 2 or 3 (AIN 2 or 3) OR anal precancer			
k) Anal Cancer			

26. Since your **last** visit, have you experienced pain in the anus caused by hemorrhoids?
    1. *Never*
    2. *Rarely*
    3. *Sometimes*
    4. *Frequently*

27. Since your **last** visit, have you had a discharge, other than blood, from your anus?
    1. *Never*
    2. *Rarely*
    3. *Sometimes*
    4. *Frequently*

28. Since your **last** visit, have you had sex with a partner whom you know had condyloma or genital warts?
    1: Yes
    0: No

[29 will only be visible if patient answered No for question 46 in the Enrolment Questionnaire]

29. Since your **last** visit, has a doctor told you that you were HIV-positive?
    1: Yes
    0: No

30. Did you see a doctor for any medical problems since your **last** survey?
    1: Yes
    0: No

[IF 30=Yes] 30.1 What condition did you see a doctor for?
[textbox 30.1]

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31. Were you diagnosed with any medical conditions since your **last** survey**?**
    1: Yes
    0: No

[IF 31=Yes] 31.1 Which medical conditions were you diagnosed with?
    [textbox 31.1]

32. Have you been hospitalized **since your last survey**?
    1: Yes
    0: No

[IF 32=Yes] 32.1 What were the reasons for your hospitalization?
    [textbox 32.1]

33. Since your **last** visit, have you injected yourself with substances or drugs?
    1: Yes
    0: No

34. Since your **last** visit, have you begun smoking regularly?
    1: Yes
    0: No

[35 will only be visible if (today's date>enrolment date + 150 AND today's date<enrolment date+210) OR (today's date>enrolment date + 330)]

35. To the best of your knowledge, which study product do you think you've been assigned?
    1. *The gel that contains carrageenan*
    2. *The gel that does not contain carrageenan*
    77. Don't know

36. To the best of your knowledge, do you think that your sex partner(s) was(were) involved in the current study?
    1: Yes
    0: No

Thank you very much for completing your follow-up survey!

All the information you have provided will be kept strictly confidential.

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Protocol for Anal Swab Collection

At each clinic visit, nurses will collect an anal swab specimen from participants for HPV testing. These will occur at months 0, 1, 2, 3, 6, 9, and 12, resulting in seven specimens in total per male.

Specimens will be collected using a Dacron™ swab.

Specimen collection materials

1. One Dacron™ applicator
2. A cone tube to hold the swab during collection
3. A Styrofoam holder to hold the vial upright during collection
4. One vial with PreservCyt
5. Gloves

Provision of instructions to participants

Men will be asked to abstain from receptive anal intercourse and anal gel use a minimum of 48 hours before specimen collection. This will minimize the risk of contamination with residual epithelial cells, urethral secretions, and/or semen.

Written instructions provided to the study nurses

1. Put on gloves.
2. Remove the Dacron™ swab from the wrapping, being very careful not to touch anything with it and place it in saline solution (to soften the cotton).
3. Ask the participant to remove their clothes from the waist down.
4. The individual will be asked to assume a comfortable position on their side (supine position) on the examination table and hold one cheek of their buttocks to the side.
5. Hold the swab three to five cm (about 1.5-2 inches) from the tip and insert it into their anus until the tip of your fingers touches the outside of their anus (at 5 cm you should feel a bit of resistance).
6. If there is too much resistance before the swab is deep enough: take away swab, then pull down skin or lift up skin and change angle of entry. If the swab has become contaminated, get a new swab.
7. Release your hold on the swab and grasp it halfway down the shaft.
8. Rotate the swab in a large circular motion, pressing gently against the sides of the anal canal.
9. Withdraw the swab gently in a twirling motion, being very careful not to touch any surface.
10. Place the swab directly into the Universal Collection Medium (UCM)-containing collection vial. Rub the swab against the inside side of the vial.

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Storage and transport

The research nurse will remove the swab from the tube, agitate the swab in the vial with PreservCyt, and then press it against the sides of the vial to express the solution. The swab is then disposed of; it is NOT stored in the vial. The vial is labeled with the participant's identifier and date. All samples will be stored in a refrigerator at 4°C pending transfer to Dr. Coutlée's laboratory. Samples will be batched and transported to the lab. At the lab, they will be stored at 4°C until being processed.

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LIMIT - HPV INSTI HIV-1 Antibody Test Procedure

**To be used by the research nurses for HIV-negative participants.

The nurse will conduct a rapid HIV test at the enrolment/baseline and at the exit visit using the INSTI HIV-1 Antibody Test Kit. This test involves using a lancet to obtain a drop of the participants blood through a finger prick.

This will be used to monitor the patient's HIV infection status throughout the clinical trial.

Be sure to read the INSTI HIV-1 Antibody Test Kit package insert before performing test.

Check test kit expiration date.

Test collection materials:

- Personal Protective Equiptment - Disposable gloves and protective eyewear
- Alcohol swab
- INSTI HIV-1 Antibody Test Kit – includes: membrane unit, sample diluent, colour developer, and clarifying solution
- Single-use Lancet
- Single-use Pipette
- Cotton Guaze

Procedure:

1. Gather materials including: alcohol swab, lancet, pipette, one sealed test pouch containing INSTI membrane unit, and one vial each of the sample diluent, colour developer and clarifying solution.
2. Wash and dry hands.
3. Put on pair of disposable gloves and protective eyewear.
4. Select a finger to perform the test. Avoid using a finger that is calloused or injured in any way. Choose a bare finger since a ring can constrict circulation.
5. Massage the finger to allow the blood to move to the surface (fingertip will become pink). The hand must be positioned at waist level or lower.
6. Clean the test area with an alcohol swab. Allow area to dry thoroughly before perfoming test.
7. As soon as the finger is dry, twist off the green protective cap from the lancet and pull it straight out. (See figure A on package insert)
8. Press the finger firmly at the point just below where the lancet will be applied.
9. Use your other hand to hold the lancet by the body and press the lancet body firmly against the finger to activate the device and to make a small puncture on the side of the test finger. (See figure B on package insert)
10. Discard the lancet in a sharps container.
11. Apply slight pressure to the distal (far end) of the finger to produce a large drop of blood.

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12. Hold the pipette horizontally and touch the tip of the pipette to the blood sample. The blood will automatically flow to the fill line and then stop. Never squeeze the tube while filling. (See figure C on package insert)
13. If you do not get enough blood to reach the fill line, gently apply intermittent pressure near the puncture site. If blood amount is inadequate, perform a second puncture using a new lancet.
14. Use guaze to have the participant apply gentle pressure to the puncture site to stop the bleeding.
15. Transfer the blood in the pipette to the Sample Diluent vial by aligning the tip of the pipette with the vial. Squeeze the pipette bulb to dispense the blood. Note: If the blood will not expel, hold the pipette vertically and slide a finger over (without pressing) the vent hole. Then squeeze the bulb. (See figure E on package insert)
16. Recap the Sample Diluent vial and mix the contents with inversion.
17. Dispose of pipette in biohazard container.
18. Tear open the pouch and carefully remove the Membrane Unit without touching the center well. The tab of the Membrane Unit can be labelled with the participants name or study ID number.
19. Place the unit on a level surface.

NOTE: At this point it is important that the following steps be performed immediately and in sequence

20. Remix the Sample Diluent/blood mixture and pour the entire contents in the center of the Membrane Unit well. NOTE: this needs to be done **within 5 minutes** of adding the blood to the Sample Diluent vial contents. The sample should be absorbed through the membrane within 30 seconds (times may vary).
21. Take the Colour Developer and slowly invert to mix the solution thoroughly.
22. Open the Colour Developer and add the entire contents to the center of the Membrane Unit well. This coloured solution should absorb through in about 20 seconds.
23. Open the Clarifying Solution and add entire contents to the center of the Membrane Unit well. This will lighten the background colour and help with reading the results.
24. Immediately read the results while the membrane is still wet. Do not allow more than 5 minutes to pass after adding the Clarifying Solution before reading results.
25. Discard all specimens and materials used for the test in a biohazard waste container.
26. Thoroughly wash hands.

Reading Results:

Please refer to the INSTI HIV-1 Antibody Test Kit package insert for diagrams and how to interpret results.

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A BLUE dot in the control spot indicates that the procedure was performed correctly and will appear on all valid tests.

Possible results include:

1. **Non Reactive (Negative)** result: only one blue dot appeas on the memberane at the Control Spot. No dot should be visible in the Test Spot (below the Control Spot).

2. **Reactive (Preliminary Positive)** result: two blue dots appear on the membrane at both the Control and Test spots. This means that the specimen contained HIV-1 antibodies. One dot may be darker than the other.

3. **Invalid Results:** (test performed incorrectly or there is a problem with the sample or device). Invalid test results need to be repeated using all new test collection materials.
    a. No dot appears on the membrane
    b. The test dot appears without the control dot
    c. There is a uniform tint across the membrane
    d. Only blue specks appear on the membrane

4. **Intermediate Results:** a faint background ring appears at the Test Spot along with the blue control dot.

If the INSTI HIV-1 Antibody test result is REACTIVE or INDETERMINATE:

Notify the participant of the test result and explain that this is a preliminary result. Another blood test will be performed and confirmed by a laboratory once he is seen by a physician.

The participant is to be referred **immediately** to Dr de Pokomandy (at MUHC Chronic Viral Illnesse Service) for follow-up.

It is important that we ensure that Dr. de Pokomandy responds and a follow-up appointment is made. (MUHC Chronic Viral Illnesses Service, tel: (514) 934-1934 Ext. 32146 - Karène Proulx-Boucher, research coordinator at the Glen site).

Explain to the participant that it is advisable to abstain from sexual activities or to use protection when engaging in sexual activities until the result can be confirmed.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	1-3, 5-8, 10-13, 16
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	1, 17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16, 17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 16, 18

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	9
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9, 10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8. 9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8, 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8, 9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8, 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8, 9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9, 11

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13, 14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13, 14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14, 15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11, 14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Appendix 3
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Appendix 3

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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BMJ Open

Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV): Design and methods for a randomized controlled trial

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Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV): Design and methods for a randomized controlled trial

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Affiliated with Clinique OPUS: Roger Leblanc; Affiliated with Clinique Médicale Urbaine du Quartier Latin: Benoit Trottier (clinical collaborators).

Affiliated with the Research Institute of the McGill University Health Centre, Montréal, Québec, Canada: Christina de Castro and Karène Proulx-Boucher (study coordination and management of subject participation); Guillaume Theriault (specimen collection).

Affiliated with the Service de Microbiologie Médicale et service d'Infectiologie, Départements de Médecine et de Biologie médicale, Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada: Julie Guénoun (HPV testing and genotyping).

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ABSTRACT

Introduction

Gay, bisexual, and other men who have sex with men (gbMSM) have an increased risk of human papillomavirus (HPV) infection and HPV-associated diseases, such as anal cancer and anogenital warts. A carrageenan-based lubricant could prevent HPV infection, thereby reducing the disease burden in this population. This paper describes the protocol for the Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV) study, an ongoing randomized controlled trial (RCT), evaluating efficacy of a carrageenan-based personal lubricant in reducing type-specific anal HPV incidence and prevalence among sexually active gbMSM, efficacy by HIV status, safety and tolerability of the gel, and participant adherence to the intervention.

Methods and analysis

The study is a double-blinded, placebo-controlled RCT. Volunteer gbMSM 18 years and older are randomly assigned 1:1 to receive the treatment (a self-applied anal microbicide gel with carrageenan) or placebo (a self-applied placebo gel). At each visit, computerized questionnaires are used to collect data on sociodemographic and clinical variables, lifestyle, sexual behaviour, and the gels' safety and tolerability. At baseline and each follow-up visit (months 1, 2, 3, 6, 9, 12), nurses collect anal specimens tested for 36 HPV types (Linear Array Assay). HIV status is determined at baseline and 12 months. The primary outcome is incidence of type-specific anal HPV infection(s) undetected at baseline. Secondary outcomes are prevalence of type-specific anal HPV infection, safety, tolerability, and adherence. We aim to recruit 380 participants to attain the study's objectives. Data will be analysed using intention-to-treat and per-protocol approaches with subgroup analyses by HIV status.

Ethics and dissemination

Ethics approval was obtained by the Research Ethics Boards of McGill University, the McGill University Health Centre (MUHC), Concordia University, and Centre Hospitalier de l'Université de Montréal (CHUM). Trial results will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number NCT02354144; Pre-results.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- First study to explore the efficacy of carrageenan as a topical microbicide for preventing anal HPV acquisition in gbMSM
- Randomized controlled trial design comparing carrageenan lubricant gel to placebo is optimal to evaluate the efficacy of carrageenan in gbMSM with and without HIV
- Due to design limitations, dosage efficacy will not be evaluated
- The exact time of HPV acquisition will be unknown
- The proportion of incident infections that could be due to reactivation of previously acquired HPV types is unknown

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INTRODUCTION

Background and rationale

Human papillomavirus (HPV) is one of the most common sexually transmitted infections worldwide.[1] A 2012 meta-analysis found that 93% of HIV-positive gay, bisexual, and other men who have sex with men (gbMSM) and 65% of HIV-negative gbMSM are currently infected with HPV.[2] Recently, an updated meta-analysis reported an HPV prevalence for HIV-positive and negative gbMSM of 81% and 47%, respectively.[3] Canadian statistics included in this meta-analysis were from a cohort study of HIV-positive gbMSM in Montreal, Quebec, which reported an HPV prevalence of 97.9%[4] and a cross-sectional study in Vancouver, British Columbia, which reported an HPV prevalence of 78.6% and 56.9% among HIV positive and negative gbMSM, respectively.[5] There is overwhelming evidence that persistent HPV infection with high oncogenic risk HPV types is the primary risk factor leading to pre-cancerous anal lesions.[6–15]

While the incidence rate of anal cancer is 1-2 per 100,000 per year,[16] the rate is 5.1 per 100,000 among HIV-negative gbMSM, and 45.9 per 100,000 among HIV-positive gbMSM, based on multinational data.[2] There is a lack of consensus on an anal screening strategy, and screening for high-grade lesions has not yet been shown to reduce the incidence of anal cancer.[17] The risk of other HPV-related lesions, such as genital warts, may decrease with condom use, but there is no consensus on whether condom use decreases the risk of HPV positivity.[18] Additionally, of the three current prophylactic HPV vaccines available, two are recommended for gbMSM[19] and offer protection from two (Gardasil®)[20] or seven (Gardasil 9®) high-risk HPV types.[21] There is thus a need for additional primary prevention measures.

Carrageenan, a gelling agent derived from red algae, is used as a stabilizer and emulsifier in food and cosmetic products.[22] Previous research demonstrated that carrageenan can block HPV transmission in vitro[23] and in animal studies.[24,25] Carrageenan interferes with virion surface proteins required for infection primarily by binding to the viral capsid thereby preventing attachment to the heparan sulfate proteoglycan receptor.[23] This interaction is long enough to allow natural inactivation of HPV by the immune system, which may increase natural HPV

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clearance. The safety and acceptability of a carrageenan-containing gel was demonstrated for vaginal[26] and vaginal and penile use.[27,28] Because of the high prevalence of HPV and the greater risk of anal cancer and its precursor lesions in gbMSM, compared to men in the general population, it is critical to determine whether a carrageenan-based lubricant can prevent HPV transmission among this at-risk group. Moreover, as carrageenan's primary mechanism of action against HPV may be affected by innate and adaptive immunity,[29] it is essential to verify if similar efficacy is observed in men with and without HIV. The aim of this paper is to describe the protocol for the 'Lubricant Investigation in Men to Inhibit Transmission of HPV Infection' (LIMIT-HPV) study, an ongoing, phase IIB, placebo-controlled, double-blinded randomized controlled trial (RCT) to evaluate the effect of a carrageenan-based lubricant on anal HPV infections in gbMSM.

Study objectives

The primary objective is to evaluate the efficacy of carrageenan in reducing type-specific anal HPV incidence, i.e., in preventing incident infections by HPV types undetected at baseline in sexually active gbMSM, overall and by HIV status. Secondary objectives are to: 1) evaluate the efficacy of carrageenan in reducing type-specific anal HPV prevalence, i.e., in accelerating clearance of existing infections in sexually active gbMSM; 2) assess the safety and tolerability of the proposed gel; and 3) assess participant adherence to the intervention.

METHODS AND ANALYSIS

Study design

LIMIT-HPV is an exploratory, phase IIB, parallel group, block-randomized, placebo-controlled, RCT with 1:1 random assignment to the treatment (a self-applied anal microbicide gel with carrageenan) or placebo (a self-applied placebo gel) group. The trial was registered on clinicaltrials.gov (NCT02354144) on February 2016. Health Canada authorized the gel for use in a clinical trial (file number 169160).

Patient and Public Involvement Statement

Prior to study initiation, a focus group was conducted to gather recommendations from 20 volunteer gbMSM and adapt our protocol accordingly. Participants answered a self-administered

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questionnaire, providing their perspective on sexual behaviour; lubricant and condom usage; candidate gels; partner's support and potential impact on compliance; sample collection; willingness to enroll in the trial, as well as other concerns and suggestions. This preliminary research in itself did not inform the research question, however, the trial design was directly impacted, e.g., participants were asked about the maximum frequency they would be willing to have an anal specimen collected, which directly informed the frequency of testing in the actual RCT. Additionally, the question of whether the sample should be nurse collected rather than self-collected was supported by 6/20 gbMSM, while 10/20 had no preference. Gel packaging was also adapted for their preferences. The recommended average monetary compensation to participate in the trial was $26.50 per visit.

Setting and recruitment

Participants are recruited at the participating clinical sites or via advertisements in various media – (classified ads on Kijiji, Craigslist, and Les Pacs; Facebook; Fugues magazine, Quebec's gay and lesbian magazine; McGill and Concordia Classifieds; an interview on McGill/Montreal CKUT Campus Community radio station; promotional videos; 'What's New' blurbs emailed to McGill students; study announcements emailed to Université de Montréal students; and class presentations) – and through printed promotional materials, including posters, business cards, posters, and button pins. Study recruitment began in February 2016 and study visits are conducted at the following clinical sites: MUHC, Clinique Médicale Urbaine du Quartier-Latin, Clinique OPUS, McGill Health Service Clinic, Concordia Health Services or at the Gerald Bronfman Department of Oncology at the Division of Cancer Epidemiology of McGill University.

Study population and procedures

Individuals are screened directly for eligibility at the clinical sites or prior to that over the telephone (Appendix 1). Alternatively, subjects interested in the study can first fill out an online, self-administered eligibility pre-enrollment questionnaire (Appendix 2). If eligible, they are contacted to confirm their eligibility and schedule the enrollment visit. Otherwise, they are emailed to thank them for their interest and explain their ineligibility.

Eligibility is based on the following criteria:

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- men aged 18 or older,
- living in Montreal and planning to remain in the city for the next 12 months,
- having had receptive anal sex with one or more men during the previous 3 months and intend to continue being sexually active for the duration of their involvement in the study, irrespective of whether their sexual partner will change,
- planning on having receptive anal sex with one or more men, but less than 50 different partners per year,
- understanding French or English,
- willing to follow study instructions and comply with follow-ups for 12 months,
- willing to do an HIV-test (for men who were never tested seropositive for HIV).

Exclusion criteria:

- participants must not be receiving treatment for anal or perianal condylomas or anal intraepithelial neoplasia lesions during the trial,
- must not have a known allergy or hypersensitivity to any of the ingredients in either gels.

Study procedures according to each visit are summarized in Figure 1. Eligible men attend an enrolment visit, where the research nurse obtains written, site-specific informed consent (Appendix 3 McGill site) and instructs the participant on proper gel use. A one-month gel supply is provided, and the first specimen is collected. The nurse also provides details about HPV infection and advice about condom use and sexual health (i.e., importance of condom use to prevent HIV and other STIs). At subsequent visits, additional bottles of gel are provided, and patients are reminded to use the gel.

Randomization and blinding

Once written informed consent is obtained and HIV status is confirmed, participants are randomized 1:1 to receive either a carrageenan-containing gel or a placebo gel. Intervention assignment occurs via a computer-assisted block randomization with randomly variable block sizes. Each participant is assigned an individual code for the duration of the study, which is used to match him to the study arm. The trial is double-blinded: participants, care providers, investigators, outcomes assessors are unaware of treatment allocation. To ensure blinding, the two gels and their containers look and feel almost identical. Additionally, four random product

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codes are assigned to the treatment gel and a different set to the control gel (eight in total) to minimize the risk of unblinding. The success of blinding is evaluated at 6 and 12 months by asking subjects to guess their assignment. If the majority guess correctly, it would suggest that blinding was ineffective.

Intervention

The intervention and placebo gels used in this trial are two commercially available gels. The differentiating feature is that one gel contains carrageenan (intervention) and the other does not (placebo). Both gels are water-based, latex-condom compatible, clear, odourless, tasteless, and have similar viscosity. Both are packaged in a plastic bottle with a disk cap that can be operated with one finger and must be applied prior to receptive anal intercourse (RAI) during the entire study period. Participants are instructed to dispense around 15 ml of the gel into the hand and apply directly to genital, anal, and condom surfaces prior to and as needed during RAI. When sexual activity ceases, the water-based formulation of the gel allows it to be easily removed with lukewarm water. Participants are asked to use the assigned gel for the entire 12 months of follow-up, independently of other methods of protection against STIs (e.g., condoms).

Adherence

To improve adherence, participants are provided with an unlimited gel supply until the end of the study. Up until April 2019, a monetary compensation of $25/visit was provided to each participant. This amount was since increased to $50 for visits 1 and 7 and $40 for visits 2-6 to better reflect the market for compensation in clinical research, to improve recruitment, and to help retain participants.

care Concomitant

The nurse informs unvaccinated individuals that the HPV vaccine has now been approved for men between 9 and 26 years of age and reminds them that protection is prophylactic and restricted to 9 vaccine-target types. In addition to the required intervention gel, we recommend condom use for the prevention of HIV and other STIs. Condoms are easily accessible: many community organizations in Montreal such as REZO, a community-based organization dedicated

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to health promotion and prevention of HIV/AIDS and other STIs, already provide condoms free of charge as a public health intervention. We also offer participants with latex allergies non-latex condoms free-of-charge that are compatible with the study gels. Condoms are available from the study nurse upon request.

Sample size

Data from the Montreal HIPVIRG cohort study of gbMSM living with HIV[4] and a multinational meta-analysis representing both gbMSM subgroups[2] informed our calculation of sample size. The reported prevalence in the HIPVIRG population[4] was very similar to studies that were conducted outside of Montreal in gbMSM living with HIV [2], justifying adopting incidence data from gbMSM without HIV from settings outside of Montreal. The technique of Dupont and Plummer was used to estimate the hazard rate of acquisition.[30] Among HIV-negative gbMSM, we estimated a conservative preventive effect size of 50% based on the expert opinion of Dr. John Schiller who discovered carrageenan's inhibitory properties (personal communication).[23] We expect a lower effect size of 30% among HIV-positive gbMSM, as carrageenan's primary inhibition mechanism relies on the immune response. The power calculations were separately tailored to satisfy our primary endpoint in each gbMSM population; however, if results are homogeneous across groups, we will consider pooling results to improve the precision of our estimates. Additionally, we specified 80% power to evaluate our primary objective with a type 1 error of 0.05 and 2-sided hypothesis. Assuming an incidence proportion of 30% at 12 months among HIV negative gbMSM[2] and accounting for 10% loss to follow-up, the sample size required for an effect size of 50% was calculated to be 270. Similarly, assuming an 85% incidence of HPV infection at 12 months among HIV-positive gbMSM[2] and accounting for 10% loss to follow-up, the estimated sample size required for an effect size of 30% was calculated to be 107. Hence, recruiting 380 participants (110 HIV-positive and 270 HIV-negative) would ensure sufficient power at the end of follow-up to assess the study's objectives. With the high frequency of new sex partners among gbMSM in a similar study by our group,[4] a 1-year follow-up period would be sufficient to allow HPV exposure opportunity and evaluate compliance.

Data collection

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The initial visit takes approximately 30 minutes, while all subsequent follow-up visits (1, 2, 3, 6, 9 and 12 months) require about 20 minutes each. Men are asked to abstain from RAI and gel use 48 hours before specimen collection to minimize the risk of contamination.[31]

Computerized questionnaire

Participants complete a self-administered baseline questionnaire at enrolment, and six follow-up questionnaires (Appendices 4 and 5, respectively). These measure HPV risk factors, compliance, and monitor the gels' safety and tolerability. Between follow-up visits, participants are asked to log into a secure web module at least once a week to answer questions on daily sexual activities, condom and study gel use, and adverse events (AE). To minimize recall bias, information can only be updated for the past 7 days (incomplete surveys expire after a week). Web-based diaries have been shown to be effective for logging sexual activities, and superior to questionnaires completed during visits for reducing recall bias.[32] This ensures high compliance and improves data quality. Responses are employed to evaluate adherence and assist in developing future studies.

Reporting AEs

To gauge the severity of AEs related to the study intervention, we refer to the Rectal Genital Grading Table for Use in Microbicide Studies[33] and Male Genital Grading Table for Use in Microbicide Studies[34]. If a stable, chronic condition is noted in the enrolment medical history questionnaire, but does not exacerbate during the trial, symptoms are recorded in the AE report but are not considered to be attributable to the gel. Subjects are advised to promptly notify the nurse of any AE; the event is documented, and the participant is triaged and treated at the discretion of the study physicians. Nonetheless, should subjects fail to immediately report an AE, they are also asked about any recent medical visits/AEs at each follow-up visit in the questionnaire.

Anal sample collection

HPV infection status is assessed by testing anal specimens. Trained study nurses collect specimens according to the Protocol for Anal Swab Collection (Appendix 6).[4] The swab

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sample is immediately preserved in PreservCyt and kept at 4°C pending transfer to Dr. Coutlée's laboratory, a WHO-accredited HPV diagnostics centre. Samples are batched and transported every 2-3 months.

HPV DNA detection and typing

The swab sample is subject to centrifugation at 13,000*g* for 15 min at 22°C; the supernatant is discarded, and the pellet is resuspended in 300µL of 20mmol/L Tris buffer (pH 8.3). DNA is purified using a Master-Pure Kit (Epicentre) and tested in each polymerase chain reaction (PCR) assay.[35] HPV detection and typing is done via the PGMY PCR protocol coupled with the Linear Array method, commercially available from Roche.[36] This test permits testing and typing for 36 different genital HPV types.[36] These types can be categorized into 3 alphapapillomavirus subgenera based on oncogenicity and tissue tropism: subgenus 1 includes low oncogenic risk types (HPVs 6, 11, 40, 42, 44, 54), subgenus 2 includes high oncogenic risk types (HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82), and subgenus 3 includes mostly commensal types (HPVs 61, 62, 71, 72, 81, 83, 84, 89).[37–40]

HIV testing

For participants who report being HIV-negative, the nurse performs a rapid HIV test at baseline and at 12 months, as is standard of care in high risk populations (Appendix 7). If positive, the participant is referred immediately to Dr. de Pokomandy at the MUHC to ensure rapid engagement with HIV care. For HIV-positive participants, a brief chart review is done at 0, 6 & 12 months to collect information on CD4 count, HIV viral load, and current antiretroviral regimen.

Loss to follow-up

Discontinuing participation of a study subject occurs if the participant voluntarily withdraws from the trial, or has AEs, illness, or other medical conditions determined by a physician to be serious enough to terminate his involvement in the study. Loss to follow-up is described as failure to reach a participant for a follow-up visit 6 months post-randomization, or the potential for a participant to jeopardize the study's integrity through protocol noncompliance.

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Outcome measures

The primary outcome is presence of a newly detected anal infection of a specific HPV type(s) in an individual who was negative for that HPV type(s) at enrolment. The secondary outcome is clearance of type-specific anal HPV infections found at baseline. Analyses will be conducted for a conservative (one negative HPV result after a positive result) and liberal (two consecutive negative results after a positive result) definition of clearance. Other secondary outcomes include participant adherence and AEs reporting.

Data management

Study and data management are facilitated through the use of a secure, password-protected web-based database to record and manage study procedures. The database is used to record participant and clinic visit information, plan visits, and export data. It is only accessible from specific IP addresses. A coded numeric system is used to identify subjects. All data, including but not limited to records, case report forms, and laboratory results remain confidential and stored in a secure location. Research staff are the only individuals with access to these personal documents. They are available to the study sponsor or participating regulatory agencies upon request. For quality control, data are downloaded from the server each month and checked for possible errors. Data management is done using SAS v9.4 (SAS Inc., Cary, NC, USA). Any missing data will be handled by multiple imputations if appropriate.

Data analysis

Analyses will be conducted separately among gbMSM with and without HIV, and pooled if appropriate. These will use intention-to-treat (i.e., including all participants who were randomized and received at least one-month's supply of gel) and per-protocol (i.e., including only "adherent" participants who complied with the protocol) approaches. Because of randomization, we expect the rates of type-specific HPV infections to be comparable between study arms at enrolment.

Primary aim 1 (prevention)

Carrageenan's efficacy will be evaluated by testing the null hypothesis of no difference in time

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to anal type-specific HPV incident infection between treatment groups using the log rank test. Time to HPV infection will be defined as the difference in days between an incident HPV detection date and time zero at enrolment. We will use Cox proportional hazards regression to estimate the hazard ratio and 95% confidence interval of HPV infection for treatment versus placebo. If the proportionality assumption is not met or the hazard ratio changes over time, we will fit a discrete-time hazards model.[41]

A sensitivity analysis will be conducted restricting to the most adherent participants in terms of gel usage. Adherence will be calculated as the number of times the gel was used during RAI divided by the number of RAIs reported in the same interval. A participant will be considered adherent if he reported, as recommended, gel use at least >50% of the time prior to every act of intercourse. Additional analyses will allow for time-varying adherence, defined as adherence since the last administered questionnaire.

Secondary aim 1 (clearance)

Time-to-event analysis techniques will be used to measure type-specific clearance of HPV infections present at enrolment, according to the intervention. Time to clearance and hazard ratios of clearance will be calculated as above.

Secondary aim 2 (Safety, tolerability, and adherence)

Safety and tolerability of the interventions will be evaluated using the AE reports from both groups. For each participant, mean adherence will be calculated for the time period between two consecutive visits and for the whole follow-up period, and it will be compared between the intervention and placebo groups using a t-test. If adherence is not normally distributed, median adherence will be compared between groups using the Mann-Whitney test. As mentioned previously, adherence will also be evaluated as a binary variable and compared between groups using the chi-square test, for each interval and overall.

Monitoring

An independent data safety monitoring board oversees the trial to ensure that it is conducted in accordance with the ethical principles of good clinical practice. The board will review the results

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of the interim analysis and make recommendations regarding safety concerns, and/or suspension or early termination of the study (e.g., unequivocal evidence of efficacy). The same board members also oversee the Carrageenan gel Against Transmission of Cervical HPV (CATCH) RCT, which is similar in design to LIMIT-HPV, however it evaluates the efficacy of a carrageenan gel among heterosexually active women.[42]

ETHICS AND DISSEMINATION

The study received ethical approval by institutional review boards of McGill University (A10-M98-14B), MUHC (2016-1434, 15-332-MUHC), Concordia University (30006074), and Centre Hospitalier de l'Université de Montréal. Protocol amendments are submitted and approved by these boards. This is the 7th study protocol version, last revised January 30th, 2019. When 50% of the targeted population (380 gbMSM) are recruited, an interim analysis will be conducted. Reports of trial findings – in the form of abstracts and manuscripts to be submitted, respectively, to peer-reviewed journals and conferences – will be presented according to the CONsolidated Standards of Reporting Trials (CONSORT) statement.[43] The co-investigators involved in the study will assist in dissemination of research findings directly to health clinics and the gbMSM community.

DISCUSSION

Presently, there is no effective way to treat anal HPV infections. With the potential for broad-spectrum anti-HPV activity, carrageenan could be a useful adjunct to HPV vaccination as a primary means of preventing HPV infections. Given the high burden of HPV infections in the gbMSM community, regular application of a carrageenan-based lubricant could be a cost-effective preventive approach, especially considering that most gbMSM regularly use lubricants for anal sex. Furthermore, treatments for condyloma and high-grade lesions are costly and often need to be repeated, as the recurrence rate is very high (particularly among people with HIV).[44] Also, vaccination is generally only maximally effective at preventing infection if administered prior to becoming sexually active.[45]

To the best of our knowledge, the LIMIT-HPV study is the first to test carrageenan against anal HPV infections. Its main strength is the blinded RCT design. Additionally, considering HIV positive and negative gbMSM would allow for the evaluation of the gel's efficacy in both

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groups. There are study limitations. An evaluation of dosage efficacy is not possible, as we do not collect information on the exact amount of gel used. While biannual[4,46–48] and annual[49–53] anal HPV sampling in longitudinal studies is common, that length of follow-up will not give sufficient detail to evaluate the study's objectives. In an ideal research setting, HPV status would be ascertained daily to have a more precise measurement of the time of HPV acquisition; however, to minimize burden on the patient, the current schedule was deemed optimal. HPV incidence is consequently interval-censored, i.e., infection date occurs sometime between the last negative and the first positive test, but the exact date is unknown. However, as the time interval between each visit is relatively short, the interval would represent an appropriate approximation. An additional limitation is the possibility that some 'incident' HPV infections are due to reactivation of previously acquired HPV, as opposed to acquisition from sexual activity.[54] However, because the proportion of incident infections that could be due to viral latency is expected to be balanced between groups as a result of (successful) randomization, the effect on the risk estimate could be biased towards the null.

The LIMIT-HPV study may show a similar protective effect as was demonstrated in an interim analysis of a related study (CATCH-RCT) conducted by our team. A reduction in the risk of incident HPV infection among participants randomized to the carrageenan gel was demonstrated, and importantly, the gels appeared safe: none of the reported AE were attributed to the gels.[42] If efficacy of the carrageenan gel is demonstrated, the current trial has the potential to improve the health of individuals in the gbMSM community by providing protection against all HPV genotypes, and ultimately reducing the risk of HPV-associated diseases in this at-risk group.

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Author's contributions

ELF, AdP, FC, and PPT conceived and designed the study. JT contributed to the grant application writing. MZ managed the study. CL drafted the manuscript under the supervision of ELF, AdP and MZ. All authors reviewed the manuscript and approved the final version.

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Declaration of interests

AdP's clinic participates in pharmaceutical clinical trials for HIV antiretrovirals and HCV treatments (ViiV Healthcare, Janssen, Merck, Gilead), received honoraria for consulting on HIV antiretroviral regimen for ViiV Healthcare, and received grants from CIHR and FRQ-S outside the submitted work.

ELF reports grants and personal fees from Merck, grants, personal fees and non-financial support from Roche, and personal fees from GSK, outside the submitted work.

JT is a Merck employee.

FC reports grants from Réseau FRQS-SIDA during the conduct of the study and grants to his institution for HPV-related work but outside of the submitted work from Merk Sharp and Dome, Roche Diagnostics and Becton Dickinson.

MZ, PPT, and CL have nothing relevant to this article to declare.

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APPENDICES
Appendix 1 - Telephone screening questionnaire
Appendix 2 - Pre-eligibility questionnaire
Appendix 3 - Informed consent form
Appendix 4 - Enrolment questionnaire
Appendix 5 - Follow-up questionnaire
Appendix 6 - Protocol for anal swab collection
Appendix 7 - HIV testing

Figure 1 legend

Potential participants are screened for eligibility based on pre-defined inclusion and exclusion criteria. Eligible participants provide informed consent and are randomized 1:1 to receive either the carrageenan-based gel or the placebo gel. They fill out an enrolment questionnaire, provide an anal HPV sample, receive a supply of the gel, are tested for HIV if HIV-negative, and a chart review is completed if HIV-positive. The participants return for each follow-up visit (months 1, 2, 3, 6, 9, 12). At follow-up visits 1 through 9, participants fill out a follow-up questionnaire, provide an HPV sample, are provided gel, and report on adverse events. At month 6 and 12, there is a blinding assessment and a chart review is completed for HIV-positive participants. At month 12, participants fill out a follow-up questionnaire, provide an HPV sample, report on adverse events, and HIV-negative men are tested again for HIV.

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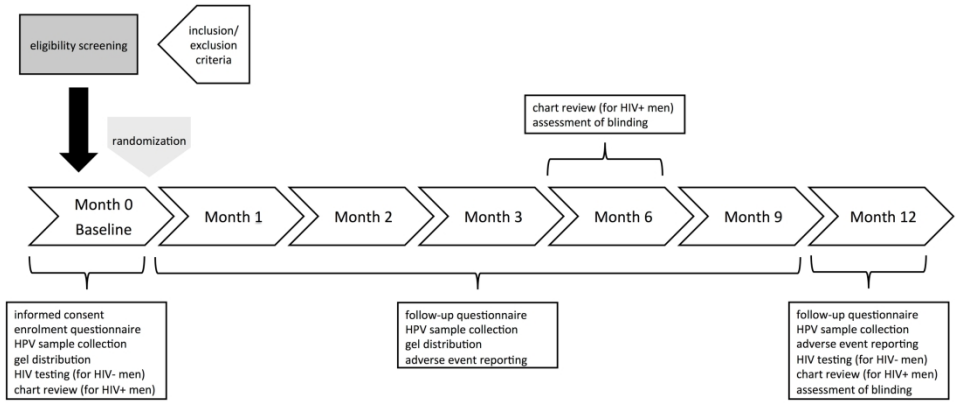

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225x127mm (300 x 300 DPI)

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LIMIT HPV Telephone Screening Questionnaire

Thank you for your interest in our study which aims at evaluating the efficacy of a lubricant gel used during receptive anal intercourse to protect against HPV infection in men having sex with men.

I will now ask you some questions to determine whether or not you are eligible. This will take about 10 minutes. Some of these questions may be of a personal nature. I would like to assure you that all your answers will be kept strictly confidential. Is that OK with you?

[Button] *Verbal consent obtained* [/Button – when pressed record date, show generated LIMIT ID at the top of the page]

1. Are you a man aged over 18 years old?
   [For programming:
   Yes [→ELIGIBLE]
   No [→ NOT ELIGIBLE]

2. For how long do you plan to stay in Montreal?
   Less than a year [→ NOT ELIGIBLE]
   A year or more [→ ELIGIBLE]

3. Are you fluent in either English or French?
   Yes [→ELIGIBLE]*No* [→ NOT ELIGIBLE]

4. How long ago did you last have receptive anal intercourse with a male partner?
   Less than 3 months ago [→ ELIGIBLE]
   3 or more months ago [→ NOT ELIGIBLE]

5. Do you think you will have receptive anal intercourse with a male partner within the next 3 months?
   Yes [→ ELIGIBLE]
   No [→ NOT ELIGIBLE]
   Don't know [→ ELIGIBLE]

6. Based on the past few years, do you expect to have less than 2 or more than 50 DIFFERENT partners in the next year?
   Yes [→ NOT ELIGIBLE]
   No [→ ELIGIBLE]

7. Eligible men must not be receiving treatment for anal or perianal condylomas or anal intraepithelial neoplasia (AIN) during the course of this study. Are you ok with this criterion?
   Yes [→ ELIGIBLE]
   No [→ NOT ELIGIBLE]

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8. Are you currently participating in another study of intervention or treatment of Human Papillomavirus (HPV) or HPV-related disease (condylomas, AIN, anogenital cancer)?
   Yes [→ NOT ELIGIBLE]
   No [→ ELIGIBLE]

9. Do you have any allergies or hypersensitivities to personal lubricants?
   Yes [→ NOT ELIGIBLE]
   No [→ ELIGIBLE]
   Don't know [→ ELIGIBLE]

10. The lubricants that we will use in this study may contain:
    Propylene Glycol
    Glycerin
    Carrageenan
    Aloe barbadensis leaf juice
    Cellulose Gum
    Citric Acid
    Diazolidinyl urea
    Saccharin
    Tetrasodium EDTA

Do you have any known allergies to any of these substances?
Yes [→ NOT ELIGIBLE]
No [→ ELIGIBLE]

[If participant status=INELIGIBLE at this point, DISPLAY SCRIPT 1 and END]
"Thank you for answering my questions. Unfortunately, you are not eligible for our study. We appreciate your interest in our study."

[IF ELIGIBLE, DISPLAY FOLLOWING QUESTIONS]
11. Thank you, I just have a few more questions.
In this study, participants will be given a lubricant gel to use during all receptive anal intercourses during one year, and will be asked to visit the clinic seven times over that year (at 0, 1, 2, 3, 6, 9 and 12 months). At each visit, a short online survey will be completed and a nurse will collect an anal swab. Participants will also keep track of their sexual activities and lubricant use through an online calendar. Do you think you will be able to follow these procedures?
Yes [→ ELIGIBLE]
No [→ NOT ELIGIBLE]

[IF 11=No, participant status=INELIGIBLE, DISPLAY SCRIPT 2 and END]
"Thank you for answering my questions. Unfortunately study participation requires the fulfillment of specific study procedures. Nonetheless, we greatly appreciate your interest in our study."

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12. So far, it looks like you are eligible for this study. Both HIV-positive and HIV-negative men are enrolled in this study. We need to know your HIV-status to see if the effect of the gel differs according to the HIV status, and to plan recruitment at the different study sites. If you never tested positive for HIV previously, we will do an HIV test by pricking your finger to obtain a drop of blood. Please choose the best answer:

    I am HIV positive [→ ELIGIBLE]
    I never tested positive for HIV before, and I am ok with doing an HIV-test for this study. [→ ELIGIBLE]
    I never tested positive for HIV before, but I am NOT ok with doing an HIV-test for this study. [→ NOT ELIGIBLE]

[IF participant status= INELIGIBLE, DISPLAY SCRIPT 2 and END]

Great, thank you for your time. So far you are eligible for the study. We can now plan your enrolment visit.

At this point, record the name, contact information and study ID number to transmit to nurse.

The Research Coordinator could also note in a separate excel sheet on where/how did the caller hear about the study (i.e., poster, Facebook ad, email, friends, etc.).

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LIMIT-HPV Study - Eligibility, Pre-screening questionnaire

(Content template for production of google form)

McGill University has several innovative research projects on Human Papillomavirus (HPV). HPV is the most common sexually transmitted disease (STD) in the world and touches more than 75% of Canadians in their lifetime.

This study investigates whether a lubricant that contains carrageenan is effective in clearing and preventing HPV infection (LIMIT study). Overall, the objective of these studies is to improve the health of ALL sexually active individuals. Results from these studies will be useful to the prevention efforts deployed in Canada as well as elsewhere in the world.

The purpose of the questionnaire below is to assess your eligibility to LIMIT. Thank you for your interest in our studies.

Best regards,

Division of Cancer Epidemiology, McGill University.

* Required

1. How did you heard about us? *

1. *Posters*
2. *Classified ads (Kijiji, AnnonceDonc, LesPacs, Craiglist, etc.)*
3. *Facebook*
4. *Word of mouth (class presentation, friends, familly, collegue)*
5. *Emails (from your department, research assistant, etc.)*

2. What is your gender? *

1. *Man*
2. *Woman*
3. *Other:*

3. What is your age? *

1. *17 years old and under*
2. *Between 18 and 45 years old*
3. *46 years old and over*

4. When was your last sexual intercourse? Here, you must specify with as much accuracy as possible the time elapsed since your last relationship (in week, month or year). *

5. Are you sexually active ? *That is, at least one sexual partner in the last 3 months. *

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1. *Yes*
2. *No*

6. Are you planning to stay in Montreal and its surrounding areas for the next year? *

1. *Yes*
2. *No*
3. *Not sure*

Additional Information

Just a few questions left!

Based on your answer, it may be possible that you're eligible for one of our studies. Please leave us your contact information, we will reach you shortly.

In all cases, we will inform you of the outcome of this questionnaire, whether you are eligible or not.

*Name (and/or nickname) **

*Phone number **

*E-mail address **

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INFORMATION AND CONSENT FORM

Research Project: Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV)

Principal investigators: Dr. Eduardo Franco and Dr. Alexandra de Pokomandy

Institution: Division of Cancer Epidemiology and Family Medicine Department, McGill University

Funding Source: The Canadian Institutes of Health Research (CIHR) and Canadian Cancer Society Research Institute (CCSRI)

You are invited to take part in a clinical trial on human papillomavirus (HPV) infection prevention. Clinical trials include only people who choose to take part. Should you decide to participate in this study, you will be given a copy of this consent form. It provides you with a detailed description of the study, describing all the procedures that will be followed. If you have any questions concerning what is explained here, do not hesitate to ask us. Please take all the time you need to read this form.

INTRODUCTION

HPV is the most common sexually transmitted infection, and most sexually active men will be infected with HPV over their lifetime. Usually these infections go unnoticed or only cause anal or genital warts (condylomas). Although benign, genital warts are difficult to treat and may lead to social embarrassment. Even if most HPV infections are temporary and will be cleared naturally, certain types cause more persistent infections that can progress to cancer.

Researchers identified that *carrageenan*, an inexpensive gelling agent that is already commonly used in food and cosmetics, is able to interfere with HPV infection. This study will examine if a personal sex lubricant containing carrageenan, directly applied to the skin and used during sexual activities, can decrease HPV infection. Such an inexpensive intervention would help reduce the burden of genital warts, and HPV-associated cancers in a cost-effective way. The gel being studied is already commercialized and sold as a personal lubricant.

PURPOSE OF THE STUDY

This study will investigate whether or not a lubricant gel that contains carrageenan is effective in preventing anal HPV infection in men who have sex with men. We will recruit 380 adult men participants in Montreal, including 110 HIV-seropositive men.

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STUDY PROCEDURE

Duration and number of visits

Your participation in this study will be for 12 months and will include 7 visits.

Table of study visits and procedures

	Visit 1 (Enrollment)	Visit 2 (1 mo)	Visit 3 (2 mo)	Visit 4 (3 mo)	Visit 5 (6 mo)	Visit 6 (9 mo)	Visit 7 (12 mo)
Questionnaire	x	x	x	x	x	x	x
Anal HPV test	x	x	x	x	x	x	x
HIV test*	x						x
Estimated duration	60 min	30 min	30 min	30 min	30 min	30 min	30 min

* For participants not known to be seropositive for HIV.

Randomization

If you are eligible and consent to enroll in this study, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor the study staff can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in Group 1 you will receive a personal lubricant that contains carrageenan.

If you are in Group 2 you will receive a personal lubricant that does not contain carrageenan.

Neither you nor the study staff will know if you are getting the carrageenan gel or the comparison gel. The reason for this is that if men know which gel they are using, it may affect what they think and say about it. If the study staff is aware of participants' group assignment, it may affect how they interpret what they see and hear in the exams and interviews. Only after the study is over will the researchers be able to find out the intervention that each participant was assigned, and whether or not the study results show a difference between the 2 groups. If you want to know which gel you were using, you will be able to find out when the whole study is finished.

Clinic Visits

You will be asked to visit the research nurse 7 times for the collection of anal specimens for HPV testing over the 12 months of your participation. At your first visit, a research nurse will provide you with instructions on how and when to apply the study gel. The nurse will collect your first anal HPV specimen in a private room at the clinic, by inserting and rotating a cotton-tip swab in your anus. This procedure is not painful, and only takes few seconds. In addition, you will be asked to complete an electronic survey. This first survey will ask questions about your background, medical and sexual history, condom and lubricant usage, smoking habits and alcohol consumption. The research nurse or coordinator will be available at all times should you need help. Before leaving, you will be provided with a one-month supply of gel. This first visit will last about one hour.

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You will visit the clinic at 1 month, 2 months, 3 months, 6 months, 9 months and 12 months after your first visit. You will be asked to abstain from receptive anal sex and gel use for at least 48 hours prior to each visit. At the clinic, the nurse will collect an anal specimen for HPV testing in a private room, and you will be asked to complete a follow-up survey about your recent sexual activities, use of study gel, and medical history. Each survey will take about 15 minutes to complete. At your one- and two-month visit, the research nurse will provide you with a one-month supply of study gel. At every visit thereafter (except for your final visit), the research nurse will provide you with 3 months' supply of gel, i.e., enough to last you until the next visit. Each visit will last about 30 minutes.

You will be asked to continue using the assigned intervention for the complete follow-up period (12 months), along with condom use for prevention of other sexually transmitted infections.

Online calendars

You will be given an access code with which you can log on to a secure internet website to complete confidential electronic calendars. You will be asked to track your sexual activities and study gel use on a weekly basis using the online calendar. The calendars will take approximately 5 minutes per week to update. Help will be available through email and telephone should you need assistance.

Laboratory testing of anal specimens

The anal specimens collected for HPV testing will be sent to the laboratory and will be tested for 36 strains of HPV, including the most common types of HPV that can cause anal cancer. HPV testing is only done for research purposes and it is not used in standard clinical care of men. Therefore, we are not planning to reveal individual test results unless specifically requested. In such a case, we can send them to your doctor at the end of your study participation. It is important to know that an HPV infection can last for a very long time. Thus, a positive test for an HPV infection does not mean that it was recently acquired.

We also ask you for permission to store the samples for future studies on HPV infection using more sophisticated techniques not yet available.

HIV status

- **If you have never been diagnosed HIV-seropositive:**
  For participants who never tested seropositive for HIV, the nurse will conduct a rapid HIV test with a drop of your blood obtained through a finger prick. We will test you at enrolment and at study exit. This will serve to verify the HIV status of participants. Please note that if your rapid test gives a HIV-seropositive result, we will need to confirm this finding with a second test using a regular blood sample and more accurate laboratory equipment. We will then ask you to abstain from sexual activities or to use protection when engaging in sex until this result can be confirmed. The nurse will immediately refer you to a physician for follow-up. If you are found to be HIV-positive at study entry (not at study exit), then the following paragraph will apply to you as well.

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- **If you are living with HIV:**
  For participants living with HIV, a review of your medical chart (at your usual HIV clinic) will be done to collect data about your HIV medical history and HIV lab results (CD4 counts, HIV viral load). We will therefore ask you to provide us with the contact information of your HIV physician.

End of study participation
Your participation in the study will be stopped early if you consider it to be in your best interest or for personal reasons, or if a physician considers it to be in your best interest because of safety reasons or your well-being.

BENEFITS
You should not expect any direct health benefits from participating in this study. While researchers hope that the intervention under study will be useful in protecting against infection with HPV, **there is no proof of this yet**. The information from this study will help researchers learn more about carrageenan as a potential treatment and preventative against anal HPV infection and anal cancer.

RISKS
Using either carrageenan or the comparison gel may cause itching, burning or pain, but these symptoms are unlikely (<5% chance). If you experience any side effects, discontinue use of the gel and contact the study nurse. Since the study gel (with or without carrageenan) does not prevent other sexually transmitted infections, you will be asked to continue using condoms for the duration of the trial.

The collection of an anal specimen for HPV testing is a safe procedure. There is a possibility of slight discomfort during the insertion of the cotton-tip swab to collect the specimen.

For the HIV-negative participants, there may be small amount of pain during the finger prick for the HIV tests. There may be psychological distress associated with testing positive for HIV. In the event that you test positive, you will receive counseling and referral for standard care.

If you experience any adverse events during your involvement in the study, you will be referred to the McGill University Student Health Services Clinic located at 3600 McTavish Street West or the MUHC Chronic Viral Illnesses Service clinic located on the 2nd floor of the MUHC Glen site 1001 Décarie.

CONFIDENTIALITY
The results from the laboratory testing of your specimens and the responses you give in the surveys will be treated with strict confidentiality. All the information that you provide online will be stored in a secure server. Only researchers who are part of the study will have access to the data. No names or other information that could identify yourself as a participant will be released. All the data from this study will be analyzed as groups without linkage of names to any data.

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The actual specimens will not be made available to investigators that are not involved with this study, nor will they be sold for commercial use. They will only be used for the purposes outlined in this consent form. They will be securely stored at University of Montreal (laboratory of co-investigator, Dr. Francois Coutlée) for as long as they are needed for the verification of laboratory results, testing with additional methods, and for research audit purposes. Your name will not be linked to any specimen.

Health Canada and the McGill University Faculty of Medicine Institutional Review Board may review the study data and files to ensure sound management of this study. For this reason, the records derived from the trial will be kept for 25 years. These records will be destroyed after 25 years.

YOUR RIGHTS

Your participation in this study is completely voluntary. You are free to withdraw from the study at any time. Your decision to withdraw will have no effect on your current or future health care. As a participant, you will be informed of any new information that may affect your willingness to participate in the trial.

By accepting to participate in this research project, you are not waiving any of your legal rights nor discharging the researchers, the sponsor or the institution, of their civil and professional responsibility.

COST

There are no costs to you, direct or indirect.

COMPENSATION

You will receive between $40 and $50 per completed study visit in compensation for costs (transport, parking, food) and/or loss of income incurred from your participation in this study. The maximum total compensation for this study (7 study visits) is $300.

ADDITIONAL INFORMATION

If at any time during your study participation you have questions about HPV or this study, you may contact one of our research staff Mrs. Natalia Morykon, at 514-398-3710 or Mrs. Karène Proulx-Boucher at 514-934-1934 extension 32146. You may also contact Dr. Mariam El-Zein, Associate Director for Research at the Division of Cancer Epidemiology, at 514-398-1489 or mariam.elzein@mcgill.ca.

If you have questions regarding your rights as a research participant, please contact Ms. Ilde Lepore, Senior Ethics Administrator of the Institutional Review Board, Faculty of Medicine at 514-398-8302 or ilde.lepore@mcgill.ca.

ETHICS APPROVAL

Health Canada has authorized the use of carrageenan for this investigational study. The McGill Institutional Review Board has reviewed this study for ethical acceptability.

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Research Project: Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV)

I. Participant's consent

I have read this consent form. I have been informed of the purpose of this study. I am aware of the study procedures and the risks and benefits of my participation. I have been informed that my participation in this study is voluntary, and that I can withdraw from this study at any time without giving a reason. I consent to take part in this study. I do not give up any of my legal rights by signing this consent form.

A dated and signed copy of the present information and consent form was given to me.

_____

Name of participant

_____ _____

Signature of participant Date

II. Signature of the person who obtained consent

I have explained the terms of the present information and consent form to the research participant and I answered all his questions.

_____

Name of person obtaining consent

_____ _____

Signature of person obtaining consent Date

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LIMIT-HPV Study - Enrolment Questionnaire
(Content template for production of computerized instrument)

IMPORTANT INFORMATION

Questions and instructions appear in regular text
Responses appear in *italicized text*
Notes and skip patterns for programming appear in [square brackets]

Questions that must be answered are marked [*REQUIRED]
All other questions are optional

For multiple choice questions, the number or letter that appears before each response option indicates the coding or numbering for the response, the number/letter is for programming purposes only and is not to appear in the participant questionnaire
Codes: 99 – skipped by the skip pattern or not applicable; 88 – left blank by the participant; 77 – don't remember/don't know

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Introduction

Thank you for being part of the study! Your participation helps us answer questions about the potential effectiveness of a Carrageenan-containing gel in reducing Human Papillomavirus (HPV) transmission.

This 30-minute survey will ask questions about you, your health and sexual history, and recent sexual behaviours. We understand that some of these questions may be sensitive and of a personal nature. We assure you that all your answers will be kept completely confidential.

There is no right or wrong answer to any question. Some questions ask you to think back over your adult years, or over the past several months, to recall specific information. Please take your time to consider each question carefully. We would greatly appreciate your efforts to answer all questions as best as you can. It is crucial for a research study to have complete and accurate information and we need your help in making this study successful.

Most questions require that you simply click on the response that applies to you. Other questions ask you to enter a specific answer, such as a number, a date, or a short text. Depending on your answer for some questions, you may be skipped past some questions. This is to save you time so that you won't have to answer questions that do not apply to you.

Ready to start? Press continue!

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General information

This part of the questionnaire concerns general information about you and where you live.

1. What is your date of birth?
   [Date field: dd/mm/yyyy - *REQUIRED]

2. In what country were you born?
   [Selection field]

[IF 2=Canada] 2.1 In which province were you born?
   [Selection field]

3. The Montreal area is made up of many ethnic groups. We would like to know in which group you would place yourself. Please indicate the most appropriate category.
   1. *French Canadian*
   2. *English Canadian*
   3. *Black Canadian*
   4. *Aboriginal*
   5. *American*
   6. *Latin American*
   7. *Haitian*
   8. *European*
   9. *African*
   10. *South Asian*
   11. *East Asian*
   12. *Middle Eastern*
   13. *Other, please specify:* [text field 3.1]

4. What is the highest degree of education that you have completed?
   1. *Less than elementary*
   2. *Elementary*
   3. *Secondary (High school)*
   4. *College or CEGEP*
   5. *University*

4.1 What is your current work or life situation?
   1: Working full time (30 hours/week or more)
   2: Working part time (<30 hours/week)
   3: On parental leave
   4: On temporary sick leave
   5: Looking for work
   6: No longer able to work
   7: No longer wish to work
   8: Other, please specify: [text field 4.1.1]

5. How long have you lived in Montreal?
   [#field] [options field 5.1- choose unit - 1: months; 2: years] *months OR years*

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Smoking History

The following questions are about your tobacco smoking habits. Please try to be as specific as possible in your answers.

6. Have you ever smoked cigarettes regularly – that is, one cigarette or more each day for a year or more?
   1: Yes
   0: No

[IF 6=No, SKIP to 10]

7. At what age did you start to smoke regularly?
   Age in years: [# field]

8. Do you still smoke regularly?
   1: Yes
   0: No

[IF 8=No] 8.1 At what age did you last stop smoking regularly?
   Age in years: [# field]

9. During your smoking years, how many cigarettes, on average, did you smoke per day?
   Cigarettes per day: [# field]

Alcohol and Drug Consumption

The next few questions are about your alcohol consumption during the **past year**. A drink refers to 1 can/bottle (375 mL) of beer, 1 glass of wine, 1 can or bottle of wine cooler, 1 cocktail, or 1 shot of liquor.

10. During the **past year**, on average, how many days per week or days per month did you have at least one drink of any alcoholic beverage?
    [#field] [options field 10.1- choose unit: per week, per month] *per week OR per month*
    0: Did not drink

[IF 10=Did not drink, SKIP to 13]

11. On the days when you drank in the **past year**, about how many drinks did you drink on average?
    Average number of drinks per drinking day: [# field]

12. Considering all types of alcoholic beverages, how many times in an average month over the **past year** did you have 5 or more drinks on an occasion?
    Times per month: [# field]
13. Have you **ever** injected yourself with substances or drugs?
    1: Yes
    0: No

[If 13 =Yes, answer 13.1 and 13.2]

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13.1 When was the **FIRST** time you ever used injection drugs (approximately)?
[date field mm/yyyy]
77: Don't remember

13.2 When was the **LAST** time you used injection drugs (approximately)?
[date field mm/yyyy]
77: Don't remember

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Lifetime Sexual History

The next questions are about your sexual history. We realize that this is a personal subject, but it is very important to the study of Human Papillomavirus (HPV). Please take the time to recall this information as accurately as possible. Some questions in this section refer to your sexual experience over your lifetime, whereas others refer only to recent experience. Please remember that all the information you give will be kept entirely confidential.

Throughout this survey, we will refer to various specific sexual acts. These terms are explained below so that everyone attaches the same meanings to them. Note that female genitals were kept in the definitions to account for sexual activities participants may have or have had with women too. Please be sure to read these definitions. If you need any further help or explanation, please ask the Research Nurse.

Oral sex:	A person's mouth on a sex partner's genital area (penis, vulva or vagina, but NOT the anus which we will refer to as rimming).
Rimming:	A person's tongue around the anus rim or in the anal canal (for this questionnaire, it includes any type of contact between a tongue and an anus).
Anal sex:	A man's penis in a sex partner's anus or rectum.
Receptive anal sex:	Being penetrated by the penis of your sex partner(s) during anal sex (being bottom).
Mutual masturbation:	Hand stimulation of a person's anal or genital area by his/her partner, NOT involving penetration of the penis in the mouth, vagina or anus.
Fisting:	Penetration of the hand (fist) in a partner's anus or rectum.
Sexual activity:	Mutual masturbation, oral sex, vaginal sex, or anal sex.
Sex partner(s):	People who have engaged in sexual activities together – whether once, or just a few times, or as regular partners, or as married partners.

14. Please think about all the people with whom you have engaged in sexual activity. In total, with how many people have you engaged in any sexual activity in your **lifetime**?
    [# field 14]
    How many were male (i.e. possessing male genitals)?
    [# field 14.1]
    How many were female (i.e. possessing female genitals)?
    [# field 14.2]

15. How old were you when you had your **first** sexual activity with a person of same sex?
    [Selection field]
16. Since you first started having sexual activities with men, with how many different men per year, on average, would you say you had sexual activities with?
    1. *None*
    2. *One per year*

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3. *2 – 5 per year*
4. *6 – 9 per year*
5. *10 – 14 per year*
6. *15 – 24 per year*
7. *25 – 49 per year*
8. *50 – 100 per year*
9. *More than 100 per year*

17. In the **last year only**, how many different male sex partners have you had?
    1. *None*
    2. *One per year*
    3. *2 – 5 per year*
    4. *6 – 9 per year*
    5. *10 – 14 per year*
    6. *15 – 24 per year*
    7. *25 – 49 per year*
    8. *50 – 100 per year*
    9. *More than 100 per year*

18. In the last **month**, have you had one or more **new** male sex partner(s)?
    1: Yes
    0: *No*

19. Do you currently have a stable male sex partner (i.e. someone with whom you have sexual activities with on a regular basis, but not necessarily an exclusive partner)?
    1: Yes
    0: *No*

[IF 19=No, SKIP to 22]

20. Do you only have anal sex with your stable male sex partner?
    1: Yes
    0: *No*

21. Does your stable male sex partner have sex with other men?
    1: Yes, or I think so
    0: *No, or I don't think so*
    77: Don't know

22. Did you ever receive fisting in your anus (i.e. penetration of your sex partner's fist in your rectum)?
    1: Yes, or I think so
    0: *No, or I don't think so*
    77: Don't know

[IF 22=Yes] 22.1 How many times in your lifetime, did you receive fisting?
[# field 14]

For the next questions, we only refer to the times you engaged in receptive anal sex.

23. Have you ever had receptive anal sex, i.e. the penis of your sex partner penetrates your anus?

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1: Yes
0: *No*

[IF 23=No, SKIP to 27]

24. In the **last year only**, how many men have you had receptive anal sex with?
    1. *None*
    2. *One per year*
    3. *2 – 5 per year*
    4. *6 – 9 per year*
    5. *10 – 14 per year*
    6. *15 – 24 per year*
    7. *25 – 49 per year*
    8. *50 – 100 per year*
    9. *More than 100 per year*

25. In the **last year only**, how often did your sex partner(s) wear a condom (rubber) when you had receptive anal sex?
    0: Never (0%)
    1: Rarely (1-24%)
    2: Occasionally (25-49%)
    3: Often (50-74%)
    4: Almost always (75-99%)
    5: Always (100%)

26. Have you ever experienced bleeding from your anus following receptive anal sex?
    1: Yes
    0: *No*

Sexual Activities in the Past Month

The next questions are about sexual activities during the past month, that is, **between dd/mm/yyyy** [CALCULATE TODAY's DATE-30] **and today**.

27. During that period, did you engage in sexual activity with one or more partner(s)?
    1: Yes
    0: No

[IF 27=No, SKIP to 47]

28. How many sex partners did you have in the **past month**?
    [# field 28]
    How many were male (i.e. possessing male genitals)?
    [# field 28.1]
    How many were female (i.e. possessing female genitals)?
    [# field 28.2]

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29. Considering all your sex partners in the **past month**, how many times in total did you engage in sexual activities? By sexual activity, we mean any of mutual masturbation, oral, vaginal, anal sex, rimming or fisting.
    [#field] [options field 29.1- choose unit – 1: per week; 2: in total] *per week OR in total*

30. In the **past month**, how many times in total did you engage in the following specific sexual activities?
    30.1 receiving oral anal (rimming), i.e. any contact between the tongue of your sex partner and your anus?
    [#field] [options field 30.1- choose unit – 1: per week; 2: in total] *per week OR in total*

    30.2 receiving fingers of your sex partner in your anus?
    [#field] [options field 30.2- choose unit – 1: per week; 2: in total] *per week OR in total*

    30.3 receiving an object (dildo/vibrator or other) in your anus or rectum (by your partner or yourself)?
    [#field] [options field 30.3- choose unit – 1: per week; 2: in total] *per week OR in total*

    30.4 receiving fisting (i.e. the fist of your partner in your anus or rectum?
    [#field] [options field 30.4- choose unit – 1: per week; 2: in total] *per week OR in total*

For the next questions, we only refer to the times you engaged in receptive anal sex.

31. With how many male partners did you engage in receptive anal sex in the **past month**?
    [#field]

32. How many times did you have receptive anal sex in the **past month**?
    [#field] [options field 32- choose unit – 1: per week; 2: in total] *per week OR in total*

33. When was the last time you had receptive anal sex?
    [date field dd/mm/yyyy]
    77: Don't remember

34. How often did you use condoms during receptive anal sex in the **past month**?
    0: Never (0%)
    1: Rarely (1-24%)
    2: Occasionally (25-49%)
    3: Often (50-74%)
    4: Almost always (75-99%)
    5: Always (100%)

[IF 34=Never, SKIP to 38]

When you used condoms for receptive anal sex (i.e. you were bottom) in the **past month**…

35. Did the condom **ever** break or slip off?
    1: Yes
    0: No
    77: Don't remember

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36. Did your partner **always** put the condom on before starting to penetrate you?
    1: Yes
    0: No
    77: Don't remember

37. Did your partner **ever** take the condom off then continued to penetrate you without the condom?
    1: Yes
    0: No
    77: Don't remember

Personal lubricants are liquids used during sexual activities to reduce friction between body parts or between body parts and other objects. We do not include saliva as a lubricant here.

38. How often did you use a lubricant when you were receiving receptive anal sex in the **past month**?
    0: Never (0%)
    1: Rarely (1-24%)
    2: Occasionally (25-49%)
    3: Often (50-74%)
    4: Almost always (75-99%)
    5: Always (100%)

39. How often did you use a lubricant during other receptive anal sexual activities in the **past month** (i.e. while you were receiving object or fisting in your anus or rectum)?
    0: Never (0%)
    1: Rarely (1-24%)
    2: Occasionally (25-49%)
    3: Often (50-74%)
    4: Almost always (75-99%)
    5: Always (100%)

[IF 38 and 39=Never/SKIPPED, SKIP to 43]

When you used lubricants in the **past month**…

40. Where did you or your partner apply the lubricant? (Mark all that apply)
    1. *Around own anus*
    2. *Inside own rectum*
    3. *On partner's penis*
    4. *Outside of the condom*
    5. *Inside of the condom*
    6. *Around partner's anus*
    7. *Inside partner's rectum*
    8. *On a sex toy that was placed on your genitals or inside your anus*
    9. *Elsewhere (please specify):* [text fields up to 3: 40.1-40.3]

41. How many teaspoons (approximate average) were used per sexual activity in the **past month**?
    1. *Greater than or equal to 1, but less than 2*
    2. *Greater than or equal to 2, but less than 3*
    3. *Greater than or equal to 3, but less than 4*

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4. *Greater than or equal to 4, but less than 5*
5. *Greater than 5*

42. What specific brand(s) of gel lubricant(s) did you use in the **past month**? (Mark all that apply)
a: Astroglide
b: Bioglide
c: ID
d: JO
e: K-Y
f: Liquid Silk
g: Maximus
h: OMY
i: Pink
j: PJUR
k: Slippery Stuff
l: Sylk
m: Uberlube
n: WET
o: *Other (please specify):* [text fields up to 3: 42.1-42.3]

Sexual Activities in the Past Week

The next questions are about sexual activities during the past 7 days, that is, **between dd/mm/yyyy** [CALCULATE TODAY's DATE-7] **and today**.

43. How many times did you have receptive anal sex with a man in the **past 7 days**?
[Drop down selection menu: numbers 0-20]

44. How many times did you use condoms during receptive anal sex in the **past 7 days**?
[Drop down selection menu: numbers 0-20]

45. How many times did you use personal lubricants during receptive anal sex in the **past 7 days**?
[Drop down selection menu: numbers 0-20]

46. How many times in total did you engage in the following specific sexual activities in the **past 7 days**?
46.1 receiving oral-anal (rimming), i.e. any contact between the tongue of your sex partner and your anus?
[Drop down selection menu: numbers 0-20]

46.2 receiving fingers of your sex partner in your anus?
[Drop down selection menu: numbers 0-20]

46.3 receiving an object (dildo/vibrator or other) in your anus or rectum (by your partner or yourself)?
[Drop down selection menu: numbers 0-20]

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46.4 receiving fisting (i.e. the fist of your partner in your anus or rectum?
[Drop down selection menu: numbers 0-20]

Medical History

The next questions ask about medical conditions or health problems you may have currently or had in the past.

47. Has a doctor **ever** told you that you were HIV-positive?
1: Yes
0: No

48. Has a doctor **ever** diagnosed you with any chronic health conditions (other than HIV)?
1: Yes
0: No

[If 48=Yes] 48.1 What chronic health conditions have you been diagnosed with (excluding HIV)?
[textbox 48.1]

49. Do you currently take any medications prescribed by a doctor [this includes medication you may take against HIV if the case]?
1: Yes
0: No

[If 49=Yes] 49.1 Please list all the medications prescribed by a doctor that you currently take
[textbox 48.1]

50. Do you have, or have you had, any allergies?
1: Yes
0: No

[If 50=Yes] 50.1 What are/were you allergic to?
[textbox 50.1]

51. Have you **ever** had surgery?
1: Yes
0: No

[If 51=Yes] 51.1 Which surgeries did you have?
[textbox 51.1]

52. Have you **ever** been hospitalized?
1: Yes
0: No

[If 52=Yes] 52.1 What were the reasons for your hospitalization(s)?
[textbox 52.1]

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53. Have you **ever** been vaccinated against HPV (i.e. with Gardasil or Cervarix)?

1: Yes
0: No

[IF 53=Yes, answer 53.1 and 53.2]

53.1 Which HPV vaccine did you receive?

1: Gardasil
2: Cervarix
3: Gardasil 9
77: Don't know or don't remember

53.2 How many vaccine doses did you receive?

[Drop down selection menu: numbers 1-3 or simple choice between 1, 2 or 3]
77: Don't know or don't remember

53.3 When was your first HPV shot?

[Date field: dd/mm/yyyy, and an open field]

54. Did a doctor **ever** tell you that you had one of the following conditions or sexually transmitted infections (STIs)?

Condition	*1:**Yes***	If yes, check if it was within the **last 6 months** [only available if yes, *0/1*]	*0: **No***	*77: **Don't know***
a) Venereal warts or condylomas				
b) Chlamydia				
c) Lymphogranuloma Venereum (LGV)				
d) Anal or genital herpes				
e) Syphilis				
f) Gonorrhea				
g) Ulcers or genital sores				
h) Hepatitis B				
i) Hepatitis C				
j) Anal high grade dysplasia OR anal intraepithelial neoplasia grade 2 or 3 (AIN 2 or 3) OR anal precancer				
k) Anal cancer				

55. In the **last five years only**, have you ever experienced pain in the anus caused by hemorrhoids?

0. Never
1. Rarely
2. Sometimes
3. Frequently

56. In the **last five years only**, have you ever had a discharge, other than blood, from your anus?

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0. Never
1. Rarely
2. Sometimes
3. Frequently

57. Have you ever had sex with a partner whom you know had condyloma or genital warts?
1: Yes
0: No

Thank you very much for your participation!

All the information you have provided will be kept strictly confidential.

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LIMIT-HPV Study – Follow-up Questionnaire
(Content template for production of computerized instrument)

For peer review only

IMPORTANT INFORMATION

Questions and instructions appear in regular text
Responses appear in *italicized text*
Notes and skip patterns for programming appear in [square brackets]

Questions that must be answered are marked [*REQUIRED]
All other questions are optional

For multiple choice questions, the number or letter that appears before each response option indicates the coding or numbering for the response, the number/letter is for programming purposes only and is not to appear in the participant questionnaire
Codes: 99 – skipped by the skip pattern or not applicable; 88 – left blank by the participant; 77 – don't remember/don't know

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Introduction

Thank you for returning to complete your follow-up questionnaire! We appreciate your continued participation.

This 20 minute survey will be asking you to update your personal and medical information, as well as your recent sexual behaviour. Please take your time to consider each question carefully. A good guess is always better than no information at all. You can leave blank any questions that you feel uncomfortable answering or do not know the answer to. We would greatly appreciate your efforts to answer all questions as best as you can.

We will also ask you about your experience with the study lubricant. Remember that you are not being evaluated on your use of the study lubricant, so please answer all questions as honestly as possible. The accuracy of this information is valuable to us.

Ready? Press continue to begin!

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Sexual Behaviour Update

The next questions are about sexual behaviour you may have engaged in since your last survey on **dd/mm/yyyy** [LAST QUESTIONNAIRE DATE].

We realize this is a personal subject, but it is very important to the study of Human papillomavirus (HPV). Please take the time to recall this information as accurately as possible. Please remember that all the information you give will be kept entirely confidential.

Throughout this survey, we will refer to various specific sexual acts. These terms are explained below so that everyone attaches the same meanings to them. Note that female genitals were kept in the definitions to account for sexual activities participants may have or have had with women too. Please be sure to read these definitions. If you need any further help or explanation, please ask the Research Nurse.

Oral sex:	A person's mouth on a sex partner's anal or genital area (penis, vulva or vagina, but NOT the anus which we will refer to as rimming).
Rimming:	A person's tongue around the anus rim or in the anal canal (for this questionnaire, it includes any type of contact between a tongue and an anus).
Anal sex:	A man's penis in a sex partner's anus or rectum.
Receptive anal sex:	Being penetrated by the penis of your sex partner(s) during anal sex (being bottom).
Mutual masturbation:	Hand stimulation of a person's anal or genital area by his/her partner, NOT involving penetration of the penis in the mouth, vagina or anus.
Fisting	Penetration of the hand (fist) in a partner's anus or rectum.
Sexual activity:	Mutual masturbation, oral sex, vaginal sex, or anal sex.
Sex partner(s):	People who have engaged in sexual activities together – whether once, or just a few times, or as regular partners, or as married partners.

1. Since your **last** survey, did you engage in sexual activity with one or more partner(s)?
   1: Yes
   0: No

[IF 1=No, SKIP to 24]

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2. How many sex partners did you have since your **last** survey?
   [# field 2]
   How many were male (i.e. possessing male genitals)?
   [# field 2.1]
   How many were female (i.e. possessing female genitals)?
   [# field 2.2]

3. Since your **last** visit, how many different male sex partners have you had?
   1. *None*
   2. *One*
   3. *2 – 5*
   4. *6 – 9*
   5. *10 – 14*
   6. *15 – 25*
   7. *More than 25*

4. Since your **last** visit, did you have at least one **new** male sex partner?
   1: Yes
   0: *No*

5. Since your **last** visit, have you had receptive anal sex (i.e. you were bottom)?
   1: Yes
   0: *No*

[IF 5=No, SKIP to 11]

6. Since your last visit, during receptive anal sex did your partner wear a condom (rubber)?
   0: Never (0%)
   1: Rarely (1-24%)
   2: Occasionally (25-49%)
   3: Often (50-74%)
   4: Almost always (75-99%)
   5: Always (100%)

[IF 6=Never, SKIP to 10]

When you used condoms for receptive anal sex **since your last survey** …

7. Did the condom **ever** break or slip off?
   1: Yes
   0: No
   77: Don't remember

8. Did your partner **always** put the condom on before starting to penetrate you?
   1: Yes
   0: No

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77: Don't remember

9. Did your partner **ever** take the condom off then continue to penetrate you without the condom?
   1: Yes
   0: No
   77: Don't remember

10. Since your **last** visit**,** have you ever experienced bleeding from your anus following receptive anal sex?
   1: Yes
   0: *No*

11. Since your **last** visit, how many times in total did you engage in the following specific sexual activities?
   11.1 receiving oral anal (rimming), i.e. any contact between the tongue of your sex partner and your anus? [#field] [options field 11.1- choose unit – 1: per week; 2: in total] *per week* OR *in total*

   11.2 receiving fingers of your sex partner in your anus?
   [#field] [options field 11.2- choose unit – 1: per week; 2: in total] *per week* OR *in total*

   11.3 receiving an object (dildo/vibrator or other) in your anus or rectum (by your partner or yourself)? [#field] [options field 11.3- choose unit – 1: per week; 2: in total] *per week* OR *in total*

   11.4 receiving fisting (i.e. the fist of your partner in your anus or rectum?
   [#field] [options field 11.4- choose unit – 1: per week; 2: in total] *per week* OR *in total*

The Study Gel

12. Since your **last** visit, have you used the study gel during sexual activities?
   1: Yes
   2: No

[IF 12=No, SKIP to 19]

13. Since your **last** visit, where did you or your partner apply the study gel during sexual activities OTHER than receptive anal sex? (Mark all that apply)
   1. *Around own anus*
   2. *Inside own rectum*
   3. *On partner's penis*
   4. *Outside of the condom*
   5. *Inside of the condom*
   6. *Around partner's anus*

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7. Inside partner's rectum
8. On a sex toy that was placed on your genitals or inside your anus
9. Elsewhere (please specify): [text fields up to 3: 13.1-13.3]

14. Since your **last** visit, have you used the study gel during receptive anal sex?
1: Yes
0: No

[IF 14=No, SKIP to 18]

15. When was the last time you used the study gel during receptive anal sex?
[date field dd/mm/yyyy]
77: Don't remember

16. During receptive anal sex, how did you or your partner apply the study gel? (Mark all that apply)
1. Around own anus
2. Inside own rectum
3. On partner's penis
4. Outside of the condom
5. Inside of the condom
6. Around partner's anus
7. Inside partner's rectum
8. On a sex toy that was placed on your genitals or inside your anus
9. Elsewhere (please specify): [text fields up to 3: 16.1-16.3]

17. How many teaspoons (approximate average) were used per round of receptive anal sex since your **last** survey?
0: Greater than or equal to 1, but less than 2
1: Greater than or equal to 2, but less than 3
2: Greater than or equal to 3, but less than 4
3: Greater than or equal to 4, but less than 5
4: Greater than 5

18. Was there anything that made it difficult for you to use (or not to use) the study gel during receptive anal sex? (Mark all that apply)
a: Application of the study gel is too difficult
b: The packaging is too inconvenient
c: You did not have the study gel on you at the time of intercourse
d: You forgot to use the study gel
e: You did not want to use lubricants
f: You preferred other brands to the study gel
g: You think that the quality of the study gel is poor (e.g., odour, feel, etc.)
h: Use of the gel caused discomfort/adverse reactions to you (please inform the nurse)
i: Partner(s) does/did not want to use lubricants
j: Partner(s) is/are allergic to ingredients of the study gel
k: Partner(s) preferred other brands to the study gel

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l: Partner(s) think(s) that the quality of the study gel is poor (e.g., odour, feel, etc.)
m: Use of the gel caused discomfort/adverse reactions to your partner(s) (please inform the nurse)
n: Other: [text fields, up to 3: 18.1-18.3]
o: Nothing, it was easy to use

19. Since your **last** survey, did you use any lubricants other than the study gel?
1: Yes
0: No

[IF 19=Yes] 19.1 What other brand(s) of gel lubricant(s) did you use **since your last survey**?
a: Astroglide
b: Bioglide
c: ID
d: JO
e: K-Y
f: Liquid Silk
g: Maximus
h: OMY
i: Pink
j: PJUR
k: Slippery Stuff
l: Sylk
m: Uberlube
n: WET
o: *Other (please specify):* [text fields up to 3: 19.1-19.3]

Sexual Activities in the Past Week

The next questions are about sexual activities during the past 7 days, that is, **between dd/mm/yyyy** [CALCULATE TODAY's DATE-7] **and today**.

20. How many times did you have receptive anal sex in the **past 7 days**?
[Drop down selection menu: numbers 0-20]

21. How many times did you use condoms during receptive anal sex in the **past 7 days**?
[Drop down selection menu: numbers 0-20]

22. How many times did you use the study gel during receptive anal sex in the **past 7 days**?
[Drop down selection menu: numbers 0-20]

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23. In the **past 7 days**, how many times in total did you engage in the following specific sexual activities?

23.1 receiving oral-anal (rimming), i.e. any contact between the tongue of your sex partner and your anus? [Drop down selection menu: numbers 0-20]

23.2 receiving fingers of your sex partner in your anus?
[Drop down selection menu: numbers 0-20]

23.3 receiving an object (dildo/vibrator or other) in your anus or rectum (by your partner or yourself)? [Drop down selection menu: numbers 0-20]

23.4 receiving fisting (i.e. the fist of your partner in your anus or rectum?
[Drop down selection menu: numbers 0-20]

Medical Update

The next questions refer to your medical history **since your last survey on dd/mm/yyyy** [LAST QUESTIONNAIRE DATE].

24. Have you received any vaccine shot against HPV (i.e. with Gardasil or Cervarix)?

1: Yes
0: No

[IF 24=Yes] 24.1 Which HPV vaccine did you receive?

1: *Gardasil*
2: Cervarix
3: Gardasil 9
77: Don't know or don't remember

24.2 How many vaccine doses did you receive?
[Drop down selection menu: numbers 1-3 or simple choice between 1, 2 or 3]
77: Don't know or don't remember

24.3 When was your first HPV shot?
[Date field: dd/mm/yyyy, and an open field]

25. Since your **last** survey, did a doctor tell you that you had one of the following conditions/sexually transmitted infections (STIs)?

Condition	*1: **Yes***	*0: **No***	*77: **Don't Know***
a) Venereal warts, condylomas, or papilloma virus infection			
b) Chlamydia			

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c) Lymphogranuloma Venereum (LGV)			
d) Genital Herpes			
e) Syphilis			
f) Gonorrhoea			
g) Ulcers of genital sores			
h) Hepatitis B			
i) Hepatitis C			
j) Anal high grade dysplasia OR anal intraepithelial neoplasia grade 2 or 3 (AIN 2 or 3) OR anal precancer			
k) Anal Cancer			

26. Since your **last** visit, have you experienced pain in the anus caused by hemorrhoids?
    1. *Never*
    2. *Rarely*
    3. *Sometimes*
    4. *Frequently*

27. Since your **last** visit, have you had a discharge, other than blood, from your anus?
    1. *Never*
    2. *Rarely*
    3. *Sometimes*
    4. *Frequently*

28. Since your **last** visit, have you had sex with a partner whom you know had condyloma or genital warts?
    1: Yes
    0: No

[29 will only be visible if patient answered No for question 46 in the Enrolment Questionnaire]

29. Since your **last** visit, has a doctor told you that you were HIV-positive?
    1: Yes
    0: No

30. Did you see a doctor for any medical problems since your **last** survey?
    1: Yes
    0: No

[IF 30=Yes] 30.1 What condition did you see a doctor for?
[textbox 30.1]

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31. Were you diagnosed with any medical conditions since your **last** survey**?**
    1: Yes
    0: No

[IF 31=Yes] 31.1 Which medical conditions were you diagnosed with?
    [textbox 31.1]

32. Have you been hospitalized **since your last survey**?
    1: Yes
    0: No

[IF 32=Yes] 32.1 What were the reasons for your hospitalization?
    [textbox 32.1]

33. Since your **last** visit, have you injected yourself with substances or drugs?
    1: Yes
    0: No

34. Since your **last** visit, have you begun smoking regularly?
    1: Yes
    0: No

[35 will only be visible if (today's date>enrolment date + 150 AND today's date<enrolment date+210) OR (today's date>enrolment date + 330)]

35. To the best of your knowledge, which study product do you think you've been assigned?
    1. *The gel that contains carrageenan*
    2. *The gel that does not contain carrageenan*
    77. Don't know

36. To the best of your knowledge, do you think that your sex partner(s) was(were) involved in the current study?
    1: Yes
    0: No

Thank you very much for completing your follow-up survey!

All the information you have provided will be kept strictly confidential.

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Protocol for Anal Swab Collection

At each clinic visit, nurses will collect an anal swab specimen from participants for HPV testing. These will occur at months 0, 1, 2, 3, 6, 9, and 12, resulting in seven specimens in total per male.

Specimens will be collected using a Dacron™ swab.

Specimen collection materials

1. One Dacron™ applicator
2. A cone tube to hold the swab during collection
3. A Styrofoam holder to hold the vial upright during collection
4. One vial with PreservCyt
5. Gloves

Provision of instructions to participants

Men will be asked to abstain from receptive anal intercourse and anal gel use a minimum of 48 hours before specimen collection. This will minimize the risk of contamination with residual epithelial cells, urethral secretions, and/or semen.

Written instructions provided to the study nurses

1. Put on gloves.
2. Remove the Dacron™ swab from the wrapping, being very careful not to touch anything with it and place it in saline solution (to soften the cotton).
3. Ask the participant to remove their clothes from the waist down.
4. The individual will be asked to assume a comfortable position on their side (supine position) on the examination table and hold one cheek of their buttocks to the side.
5. Hold the swab three to five cm (about 1.5-2 inches) from the tip and insert it into their anus until the tip of your fingers touches the outside of their anus (at 5 cm you should feel a bit of resistance).
6. If there is too much resistance before the swab is deep enough: take away swab, then pull down skin or lift up skin and change angle of entry. If the swab has become contaminated, get a new swab.
7. Release your hold on the swab and grasp it halfway down the shaft.
8. Rotate the swab in a large circular motion, pressing gently against the sides of the anal canal.
9. Withdraw the swab gently in a twirling motion, being very careful not to touch any surface.
10. Place the swab directly into the Universal Collection Medium (UCM)-containing collection vial. Rub the swab against the inside side of the vial.

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McGill

Storage and transport

The research nurse will remove the swab from the tube, agitate the swab in the vial with PreservCyt, and then press it against the sides of the vial to express the solution. The swab is then disposed of; it is NOT stored in the vial. The vial is labeled with the participant's identifier and date. All samples will be stored in a refrigerator at 4°C pending transfer to Dr. Coutlée's laboratory. Samples will be batched and transported to the lab. At the lab, they will be stored at 4°C until being processed.

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LIMIT - HPV INSTI HIV-1 Antibody Test Procedure

**To be used by the research nurses for HIV-negative participants.

The nurse will conduct a rapid HIV test at the enrolment/baseline and at the exit visit using the INSTI HIV-1 Antibody Test Kit. This test involves using a lancet to obtain a drop of the participants blood through a finger prick.

This will be used to monitor the patient's HIV infection status throughout the clinical trial.

Be sure to read the INSTI HIV-1 Antibody Test Kit package insert before performing test.

Check test kit expiration date.

Test collection materials:

- Personal Protective Equiptment - Disposable gloves and protective eyewear
- Alcohol swab
- INSTI HIV-1 Antibody Test Kit – includes: membrane unit, sample diluent, colour developer, and clarifying solution
- Single-use Lancet
- Single-use Pipette
- Cotton Guaze

Procedure:

1. Gather materials including: alcohol swab, lancet, pipette, one sealed test pouch containing INSTI membrane unit, and one vial each of the sample diluent, colour developer and clarifying solution.
2. Wash and dry hands.
3. Put on pair of disposable gloves and protective eyewear.
4. Select a finger to perform the test. Avoid using a finger that is calloused or injured in any way. Choose a bare finger since a ring can constrict circulation.
5. Massage the finger to allow the blood to move to the surface (fingertip will become pink). The hand must be positioned at waist level or lower.
6. Clean the test area with an alcohol swab. Allow area to dry thoroughly before perfoming test.
7. As soon as the finger is dry, twist off the green protective cap from the lancet and pull it straight out. (See figure A on package insert)
8. Press the finger firmly at the point just below where the lancet will be applied.
9. Use your other hand to hold the lancet by the body and press the lancet body firmly against the finger to activate the device and to make a small puncture on the side of the test finger. (See figure B on package insert)
10. Discard the lancet in a sharps container.
11. Apply slight pressure to the distal (far end) of the finger to produce a large drop of blood.

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12. Hold the pipette horizontally and touch the tip of the pipette to the blood sample. The blood will automatically flow to the fill line and then stop. Never squeeze the tube while filling. (See figure C on package insert)
13. If you do not get enough blood to reach the fill line, gently apply intermittent pressure near the puncture site. If blood amount is inadequate, perform a second puncture using a new lancet.
14. Use guaze to have the participant apply gentle pressure to the puncture site to stop the bleeding.
15. Transfer the blood in the pipette to the Sample Diluent vial by aligning the tip of the pipette with the vial. Squeeze the pipette bulb to dispense the blood. Note: If the blood will not expel, hold the pipette vertically and slide a finger over (without pressing) the vent hole. Then squeeze the bulb. (See figure E on package insert)
16. Recap the Sample Diluent vial and mix the contents with inversion.
17. Dispose of pipette in biohazard container.
18. Tear open the pouch and carefully remove the Membrane Unit without touching the center well. The tab of the Membrane Unit can be labelled with the participants name or study ID number.
19. Place the unit on a level surface.

NOTE: At this point it is important that the following steps be performed immediately and in sequence

20. Remix the Sample Diluent/blood mixture and pour the entire contents in the center of the Membrane Unit well. NOTE: this needs to be done **within 5 minutes** of adding the blood to the Sample Diluent vial contents. The sample should be absorbed through the membrane within 30 seconds (times may vary).
21. Take the Colour Developer and slowly invert to mix the solution thoroughly.
22. Open the Colour Developer and add the entire contents to the center of the Membrane Unit well. This coloured solution should absorb through in about 20 seconds.
23. Open the Clarifying Solution and add entire contents to the center of the Membrane Unit well. This will lighten the background colour and help with reading the results.
24. Immediately read the results while the membrane is still wet. Do not allow more than 5 minutes to pass after adding the Clarifying Solution before reading results.
25. Discard all specimens and materials used for the test in a biohazard waste container.
26. Thoroughly wash hands.

Reading Results:

Please refer to the INSTI HIV-1 Antibody Test Kit package insert for diagrams and how to interpret results.

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A BLUE dot in the control spot indicates that the procedure was performed correctly and will appear on all valid tests.

Possible results include:

1. **Non Reactive (Negative)** result: only one blue dot appeas on the memberane at the Control Spot. No dot should be visible in the Test Spot (below the Control Spot).

2. **Reactive (Preliminary Positive)** result: two blue dots appear on the membrane at both the Control and Test spots. This means that the specimen contained HIV-1 antibodies. One dot may be darker than the other.

3. **Invalid Results:** (test performed incorrectly or there is a problem with the sample or device). Invalid test results need to be repeated using all new test collection materials.
    a. No dot appears on the membrane
    b. The test dot appears without the control dot
    c. There is a uniform tint across the membrane
    d. Only blue specks appear on the membrane

4. **Intermediate Results:** a faint background ring appears at the Test Spot along with the blue control dot.

If the INSTI HIV-1 Antibody test result is REACTIVE or INDETERMINATE:

Notify the participant of the test result and explain that this is a preliminary result. Another blood test will be performed and confirmed by a laboratory once he is seen by a physician.

The participant is to be referred **immediately** to Dr de Pokomandy (at MUHC Chronic Viral Illnesse Service) for follow-up.

It is important that we ensure that Dr. de Pokomandy responds and a follow-up appointment is made. (MUHC Chronic Viral Illnesses Service, tel: (514) 934-1934 Ext. 32146 - Karène Proulx-Boucher, research coordinator at the Glen site).

Explain to the participant that it is advisable to abstain from sexual activities or to use protection when engaging in sexual activities until the result can be confirmed.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	1-3, 5-8, 10-13, 16
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	1, 17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16, 17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 16, 18

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	9
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9, 10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8. 9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8, 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8, 9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8, 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8, 9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9, 11

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13, 14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13, 14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14, 15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11, 14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Appendix 3
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Appendix 3

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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