Role of host cell DNA Methylation Analysis in predicting non-Regression or regression of high-grade anal Intraepithelial NEoplasia in HIV+ men (MARINE) trial

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON22302

Source
Nationaal Trial Register

Brief title
MARINE-trial

Health condition

Anal cancer, anal intraepithelial neoplasia, HPV

Sponsors and support

Primary sponsor: Amsterdam UMC, location AMC
Source(s) of monetary or material Support: Amsterdam UMC, location AMC

Intervention

Outcome measures

Primary outcome

The primary endpoint is the regression or non-regression dichotomy of each individual HGAIN lesion at baseline based on the histological outcome of the 24-months follow-up anal biopsy. The histological outcome is based on the LGAIN/HGAIN dichotomy according to the criteria, terminology and recommendations of the Lower Anogenital Squamous Terminology (LAST) Project. To follow-up each individual HGAIN lesion, its location is recorded along 8 segments (octants) along the circular transformation zone in the anal canal. Regression is defined as any biopsy-proven LGAIN, or no AIN lesion in the octant of a HGAIN lesion previously seen at baseline, or in one of the adjacent octants. If no lesion is visible upon HRA at 24 months, a biopsy is obtained at random from the octant where the HGAIN lesion was seen at baseline. HGAIN non-regression is defined as any biopsy-proven HGAIN lesion or anal cancer in the octant of a HGAIN lesion previously seen at baseline, or in one of the adjacent octants .

Secondary outcome

Secondary outcomes are to assess:
• The histological outcome of each individual HGAIN lesion at the 6-, 12-, and 18-month follow-up visits.
• The clinical outcome of each individual HGAIN lesion at the 6-, 12-, 18-, and 24-month follow-up visits, defined as a change in size measured by the number of octants of the anal surface affected.
• Overall HGAIN disease: the highest histological outcome of all HGAIN lesions combined at the 6-, 12-, 18, and 24-month follow-up visits.
• Overall HGAIN disease: the clinical outcome of all HGAIN lesions combined at the 6-, 12-, 18-, and 24-month follow-up visits, defined as a change in size of any HGAIN lesion , measured by the number of octants of the anal surface affected, including incident HGAIN lesions during, and in between follow-up visits.
• Health-related quality of life (HRQoL) in the study group compared to the HRQoL control group at baseline, and at the 6- and the 24-month follow-up visits.

Study description

Background summary

Rationale: Human papillomavirus (HPV)-induced anal cancer precursors, high-grade anal intraepithelial neoplasia (HGAIN), are known to have a spontaneous regression rate of 28%. Current histopathological assessment is unable to distinguish between HGAIN likely to regress and HGAIN likely to persist or progress to cancer. To prevent anal cancer, currently all HGAIN is treated by electrocautery, which leads to substantial overtreatment.
Objective: In this study we will clinically validate if previously identified promising host cell DNA methylation markers and other biomarkers can predict (non-)regression of HGAIN, thus determining the need of immediate treatment versus active surveillance, and the safety of withholding treatment. This could prevent overtreatment and the associated anal and psycho-sexual morbidity, thus improving anal cancer screening efficacy and quality of life of HIV+ MSM.

Study design: A multicentre active monitoring cohort study in Amsterdam, the Netherlands, in which HIV+ MSM with HGAIN will not be treated during a 24-months follow-up.
Study population: HIV+ MSM (n=200) diagnosed with HGAIN (<50% of anal circumference) will be recruited.
Intervention: Participants will be monitored by six-monthly high-resolution anoscopy (HRA) with biopsies and anal swabs for cytology. Baseline tissue samples will be tested with host cell DNA methylation markers (ASCL1, ZNF582) and other biomarkers: HPV genotyping, HPV-E4, p16INK4A, Ki-67, and immunological markers.
Main study parameters/endpoints: The primary study endpoint is regression or nonregression of each individual HGAIN lesion at the end of the study, based on the histopathological outcome. Regression and non-regression are defined as respectively ≤LGAIN and ≥HGAIN in the exit biopsy at 24 months, taken within the same octant or shifted up to one octant on either side of the baseline lesion.
Main secondary endpoints are: clinical outcome, reflected as the number of octants affected by each individual HGAIN lesion, overall disease: the histological and clinical outcomes of all HGAIN lesion combined; and the health-related quality of life (HRQoL) of the study population compared to a control group of 50 HIV+MSM receiving HGAIN treatment.
We will calculate regression rates in lesions with low versus high methylation levels at baseline.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participating patients will be withheld potential treatment for anal cancer prevention. Currently, treatment of HGAIN for anal cancer prevention is not yet evidencebased.
Efficacy of treatment is suboptimal and patients experience considerable side effects.
We therefore already offer patients the possibility to choose between active monitoring at a similar interval or treatment.
The associated risk of this study is acceptable because: (1) the study follow-up will be two years, and the risk of progression to cancer will be particularly low in that period, (2) patients at very high risk for cancer (i.e. patients with more than 50% of anal canal affected, patients with clinical suspicion for cancer and with abnormalities on digital ano-rectal examination (DARE) plus MRI) will not be included and (3) participants will be closely monitored during the trial and excluded for treatment when clinical suspicion for cancer arises.

Study objective

The hypothesis is that methylation marker panel, potentially combined with additional biomarkers, can predict (non-)regression of HGAIN, thus determining the need of immediate treatment versus active surveillance, and the safety of withholding treatment. This could prevent overtreatment and the associated anal and psycho-sexual morbidity, and improve anal cancer screening efficacy and quality of life of HIV+ MSM.

Study design

The primary outcome will be measured at the 24-month follow-up visit and compared to baseline findings using the histological outcome of the biopsies taken during HRA, as described above. The secondary outcomes will be measured at the 6-, 12-, 18-, and 24-month

follow-up visits and compared to baseline findings using the histological outcome of the biopsies taken during HRA and the clinical outcome observed during HRA, defined as a change in size measured by the number of octants of the anal surface affected. The HRQoL will be measured at baseline, 6- and 12-month follow-up using the ANCHOR Health-Related Symptom Index (A-HRSI), which is a validated assessment form specifically designed for our target population.

Intervention

At baseline socio-demographic, medical, AIN, HIV, and sexual history will be recorded in an electronic Case Report Form (eCRF). At baseline and at six-monthly (±2 weeks) visits, during a total follow-up of 24-months, participants will undergo an anal swab, digital anal-rectal examination (DARE) and HRA (including photo documentation) after at least 1-2 minutes application of acetic acid (5% solution), followed by repeated application during the exam, and biopsies of all suspected lesions after staining with Lugol's iodine when indicated by experienced HRA providers adhering to the International Anal Neoplasia Society Guidelines. Lesion characteristics, localisation and size will be recorded.

Anal swab specimens will be collected using a wetted nylon-flocked swab, that will be slowly retracted after insertion while rotating and applying firm lateral pressure, and transferred and stored in ThinPrep PreservCyt Solution (Hologic, Marlborough, Massachusetts, USA). Anal cytology will be performed as a quality control measure: in case of an indication for a high-grade lesion on cytology while no high-grade lesions were found at HRA, the HRA will be repeated to make sure no lesions were missed. Residual anal swab specimens will be stored at -20°C.

At the last follow-up visit, an exit biopsy is taken from every lesion, or at random if there is no visible lesion at the location of the previous lesion. After the 24-month follow-up visit patients will return to standard care.

For safety and per standard of care, clinical suspicion of cancer and/or palpable abnormalities found using DARE will be followed up with MRI to rule out progression to cancer. In case of invasion seen at MRI, or in a biopsy obtained during a follow-up HRA, the participant will be excluded from the study, for treatment of anal cancer (cancer will then be diagnosed at a very early stage) according to local guidelines.

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Eligibility criteria

Inclusion criteria

- HIV+ patients of at least 18 years of age that are cisgender men, transgender men or transgender women and who have sex with men (further referred to as HIV+ MSM);
-- Transgender men and women are an often neglected group in research, but also at risk for anal HPV . Because of the comparable risk profile, we assume that HIV+ transgender men and women who have sex with men have a comparable chance of progression to anal cancer as cisgender HIV+MSM.
- histopathological confirmed HGAIN (≥1 lesion);
- satisfactory HRA at baseline, i.e. visualisation of entire transformation zone with biopsies of all lesions;

Exclusion criteria

- HGAIN covering >50% of the circumference of the anal canal (progression to cancer of these patients is estimated as high and therefore withholding treatment would be unethical);
- clinical suspicion for anal cancer, defined as palpable abnormalities at DARE and suspicion of invasion at MRI;
- histopathological diagnosis of anal cancer;
- history of anal cancer;
- previous HPV vaccination (including participants of the VACCAIN-T and VACCAIN-P trial);
- concomitant cancer;
- insufficient Dutch or English language skills.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non controlled trial

Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	05-09-2021
Enrollment:	200
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion

Date:	03-08-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL9664
Other	METC AMC : METC 2021_099

Study results