Role of host cell DNA methylation analysis in predicting non-regression or regression of high-grade anal intraepithelial neoplasia in HIV+ men trial (MARINE)

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In this study we clinically validate if host cell DNA methylation markers 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...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Anal and rectal conditions NEC
Study type	Observational invasive

Summary

ID

NL-OMON54464

Source
ToetsingOnline

Brief title
MARINE

Condition

- Anal and rectal conditions NEC
- Viral infectious disorders
- Skin neoplasms malignant and unspecified

Synonym
Anal Cancer Precursors, High Grade Anal Intraepithelial Neoplasia

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: anal cancer, anal intraepithelial neoplasia (AIN), Host cell DNA methylation markers, human papillomavirus (HPV)

Outcome measures

Primary outcome

• The primary endpoint is the regression / non-regression dichotomy of each

individual HGAIN lesion at baseline.

• The primary endpoint is based on the histological outcome of the 24-months

follow-up anal biopsies from each individual HGAIN lesion.

• The histological outcome is based on the LGAIN/HGAIN dichotomy according to

the LAST criteria.

• 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 an individual HGAIN lesion previously seen at baseline, or in one of

the adjacent octants.

• If no clinical lesion is visible upon HRA at 24 months, a biopsy is obtained

at random form the octant where the individual HGAIN lesion was previously seen

at baseline.

• HGAIN non-regression is defined as any biopsy-proven HGAIN lesion or anal

cancer in the octant of an individual HGAIN lesion previously seen at baseline,

or in one of the adjacent octants.

For the substudy, endpoints are:

1. To determine the frequency and phenotype of CXCR3+ TRMs in AIN lesions of HIV-positive and HIV-negative individuals.

2. To identify HIV-specific altered immune pathways associated with CXCR3 expression, tumor progression, and/or aberrant immune responses to HPV at the single-cell level.

3. To validate the presence and functional relevance of cTRMs in HPV by characterizing their clone sequence and phenotype in pre-cancerous lesions.

4. To identify hot-spots of intensive HPV antiviral defense and cell-cell interaction in the pre-cancerous lesion at the sub-compartmental level using imaging and transcriptomic approaches.

Secondary outcome

Secondary endpoints are:

• 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 the size measured by the number of octants of the anal surface affected

• 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 the 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.

• Overall HGAIN disease: the histological outcome of all HGAIN lesions combined at the 6-, 12-, 18, and 24-month follow-up visits.

• HRQoL of the study population compared to the control population at baseline, the 6- and the 24-month follow-up visit.

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3. To validate the presence and functional relevance of cTRMs in HPV by characterizing their clone sequence and phenotype in pre-cancerous lesions.

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Study description

Background summary

Human Papillomavirus (HPV)-induced anal cancer precursors, high-grade anal intraepithelial neoplasia (HGAIN), are known to have a high spontaneous regression rate. 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.

Study objective

In this study we clinically validate if host cell DNA methylation markers 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, improving anal cancer screening efficacy and quality of life of HIV+ MSM.

Furthermore, in a subset of patients we aim to understand the role of CXCR3+ tissue resident effector memory T cells (TRMs) in HGAIN and identify new immunological pathways that could lead eventually to new therapeutic approaches, and prognostic markers in HIV+ patients affected by AIN.

Study design

We initiate a multicentre active monitoring cohort study in Amsterdam, the Netherlands, in which HGAIN lesion will not be treated during a 24-months follow-up. Participants will be monitored by six-monthly High-Resolution Anoscopy (HRA) with biopsies and anal swabs for cytology. Baseline samples will be tested with host cell DNA methylation markers (ASCL1, SST, ZNF582) and possibly other biomarkers (HPV genotyping, HPV-E4, p16INK4A, Ki-67 and PD-1/PD-L1). Participants of both the study group and the HRQoL control group will be asked to fill in the validate A-HRSI questionnaire to measure the health-related quality of life (HRQoL).

In a subset of patients (further referred to as substudy), a cross-sectional analysis on HGAIN biopsies will be performed. During their regular treatment visit, participants will undergo two additional biopsies after local anaesthesia and before electrocoagulation. Besides, participants will undergo a phlebotomy.

Study burden and risks

Participating patients will be withheld of treatments for anal cancer prevention. The associated risk is acceptable because treatment for HGAIN for anal cancer prevention is not yet evidence-based. Efficacy of treatment is suboptimal and patients experience considerable side-effects. Currently, we already offer patients the possibility to choose for active monitoring or treatment. Furthermore, since the study follow-up will be two years, the risk of cancer development will be particularly low, and 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 DARE plus MRI) will not be included at the start. Participants will be closely monitored

during the trial and excluded for treatment when clinical suspicion for cancer arises.

Substudy participants indicated for electrocautorization of HGAIN lesions will receive two additional biopsies prior to the treatment procedure. Since participants will undergo the biopsies after local anaesthesia and before the electrocoagulation treatment, the additional discomfort, blood loss, and pain from the experimental biopsies will be neglible. In addition, two times 10 ml of peripheral blood will be collected via phlebotomy. This substudy will allow us to closely scrutinize immunological mechanisms such as the activation of CXCR3+ in HGAIN lesions in HIV+ patients, potentially finding leads for new biomarkers and therapeutics.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Study group (N=200) - 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); - histopathological confirmed HGAIN (>=1 lesion); - satisfactory HRA at baseline, i.e. visualisation of entire transformation zone with biopsies of all lesions; Substudy HIV-positive group (N=20): - >18 years of age - Compliance to ART, undetectable viral load since at least 1 year - A low nadir CD4 cell count (<200 cell/µl) - Histopathologically confirmed HGAIN (>=1 lesion); - Satisfactory HRA at baseline, i.e. visualisation of entire transformation zone with biopsies of all lesions; Substudy HIV-negative group (N=20) - >18 years of age - Histopathologically confirmed HGAIN (>=1 lesion); - Satisfactory HRA at baseline, i.e. visualisation of entire transformation zone with biopsies of all lesions;

Exclusion criteria

Study group: - HGAIN covering more than 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. Substudy group (N=40): - 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); - Known active chronic infection such as hepatitis B or C - Diabetes mellitus - Insufficient Dutch or English language skills. - Presence of any diseases affecting the anal mucosa (fistulas, rhagades, eczema). - Signs of current STI.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-08-2021
Enrollment:	240
Type:	Actual

Ethics review

Approved WMO Date:	12-07-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	18-07-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214

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Approved WMO Date:	24-05-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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
CCMO	NL76718.018.21
Other	NL9664