Treatment of anal intraepithelial neoplasia in HIV-positive patients, a triple-arm randomized clinical trial

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To establish the preferred treatment of AIN to prevent the development of severe anal neoplasia (persistent AIN III or anal carcinoma) in HIV+ MSM and HIV+ woman.

Ethical review	Approved WMO
Status	Pending
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON32379

Source
ToetsingOnline

Brief title
Treatment of AIN in HIV+ patients

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Skin neoplasms malignant and unspecified

Synonym
anal dysplasia

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 intraepithelial neoplasia, HIV, Human papilloma virus

Outcome measures

Primary outcome

Histological resolution of AIN 4 weeks after the end of treatment and relapse

rate at 24, 48 and 72 weeks after treatment.

Secondary outcome

- Side effects of treatment

- QALY*s, derived from the EQ-5D questionnaire

- Questionnaire sexual functioning: FSFI and IIEF -

- Costs of local treatment of precancerous lesions to prevent severe anal

neoplasia

- HPV types and HPV load before and after treatment

- Single nucleotide polymorphisms (SNPs)in genes involved in the recognition of

pathogens and the inflammatory response

- Presence of sexual transmitted co-infections

Study description

Background summary

Due to effective antiretroviral treatment (HAART), overall HIV/AIDS related mortality has decreased. However, as a result of the increased life span new causes of morbidity and mortality have become important. Several malignancies, in particular anal carcinoma, are observed in excess in HAART-treated HIV patients: the relative risk of anal carcinoma in HAART-treated HIV+ homosexual men (MSM) is 352 as compared to HIV-negative men. Like in cervical cancer, the development of anal carcinoma appears to require infection with oncogenic HPV types. Precancerous anal lesions (Anal Intraepithelial Neoplasia, graded AIN I

to AIN III), are present in a large proportion (over 50%) of HIV+ MSM and women, and sensitive and specific screening methods are available.
As the annual incidence of invasive anal carcinoma in this group exceeds by far (224 vs. 10 per 100.000 persons at risk) the incidence of cervical cancer in HIV-negative women, for whom regular cervical screening is standard-of-care, this suggests that HIV+ MSM and women should be screened regularly and their preneoplastic lesions be treated.
However, at this stage the optimal treatment of precancerous lesions is insufficiently known. Electro-coagulation is standard-of-care, but local imiquimod treatment was better tolerated and showed a 77% clinical and histological clearance and a low recurrence rate. Also treatment with fluorouracil crème shows promising results. However, these treatment modalities have not been evaluated in a head-to-head comparison.

Study objective

To establish the preferred treatment of AIN to prevent the development of severe anal neoplasia (persistent AIN III or anal carcinoma) in HIV+ MSM and HIV+ woman.

Study design

In this study, we will screen 300 HIV+ MSM and women treated at the HIV outpatient clinics of the AMC, at two consecutive years, by performing high resolution anoscopy (HRA) using a colposcope. Besides anal swabs for HPV-typing, biopsies will be taken in if suspicious lesions are seen,. In this case also biopsies of healthy tissue are taken for studies regarding local immunity.
In case of AIN I-III in anal biopsies patients will be randomized (1:1:1) between three treatment regimens: local treatment of lesions with fluorouracil, imiquimod or with electro-coagulation. Treatment duration is 16 weeks. Imiquimod is applied three times a week, fluorouracil twice a week. Coagulation is repeated every 4 weeks when lesions persist.
Four weeks after treament early efficacy is evaluated by HRA and biopsies. Follow up is at 24, 48 and 72 weeks after treatment.

Intervention

Treatment-arm 1: electro-coagulation during high resolution anoscopy, repeated every 4 weeks if necessary
Treatment-arm 2: imiquimod (Aldara-creme), 3 times a week, applied by the patient
Treatment-arm 3: fluorouracil (Efudix-creme), twice a week, applied by the patient

Study burden and risks

Patiënts will have to come to the outpatient clinic at least twice, maximum 11 times. The visits will take aproximately thirty minutes. At part of these visits high-resolution anoscopy (HRA) will be performed, which is inconvenient for the patient. A bloodsample will be taken, which can cause discomofort, like bruising.
A very rare complication of taking biopsies and coagulation is perforation. Coagulation can sometimes be painful and can cause scaring which can lead to narrowing of the anus. Adverse effects of imiquimod and fluorouracil are minor. Both cause normally redness of the skin where applied. A burning feeling can occur. Sometimes little erosions are seen with bleeding. In rare cases fluorouracil can cause narrowing of the anus. Eightteen percent of patients treated with imiquimod report flu-like symptoms during the first two weeks of treatment. Patients are instructed to refrain from anal intercourse for eight hours after application of fluorouracil (twice a week) and imiquimod (three times a week).

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

- Patient is * 18 years of age
- Patient has a proven HIV infection
- Patient is MSM or woman.

Exclusion criteria

- History of anal carcinoma
- History of chronic bowel disease
- Life expectancy < 12 months
- Pregnancy or lactation
- Active i.v. drug use

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2008
Enrollment:	150
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Aldara
Generic name:	Imiquimod
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Efudix
Generic name:	fluoruracil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-06-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2007-006277-92-NL
CCMO	NL20042.018.07