Novel therapies for HPV-related anal disease

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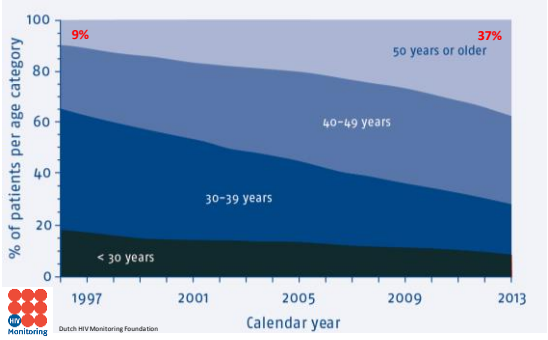
Increasing Age in HIV



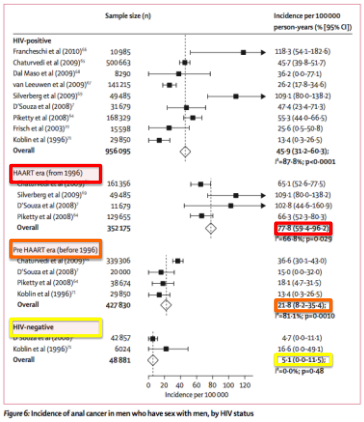


Figure 6: Incidence of anal cancer in men who have sex with men, by HIV status

HPV associated Anal Cancer Incidence In MSM per 100,000 py

Machalek et al, Lancet Oncology 2012

Low nadir CD4, alcohol use, and smoking are significantly associated with anal cancer in HIV+ MSM

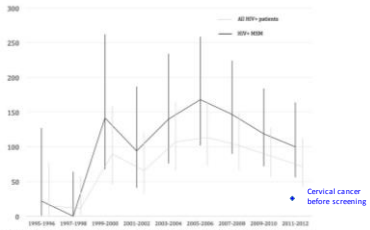
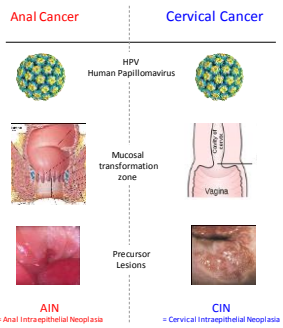
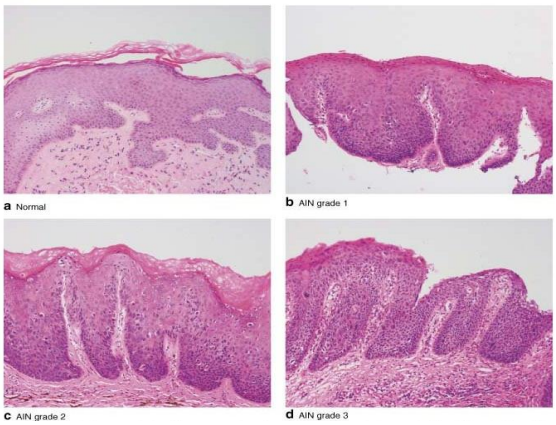


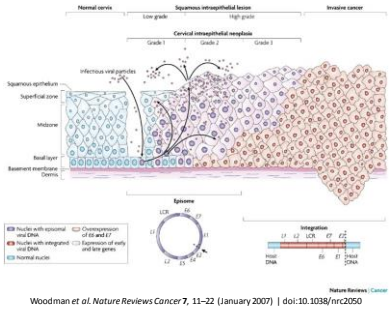
FIGURE 1. Anal cancer incidence per 100,000 person-years (with 95% CIs) for 9 consecutive 2-year blocks in all HIV+ patients and HIV+ MSM separately in the Netherlands (1995–2012).

Richel et al, JAIDS, 2015





AIN progression



Woodman *et al. Nature Reviews Cancer* **7**, 11–22 (January 2007) | doi:10.1038/nrc2050

AIN prevalence

AIN prevalence in HIV+ MSM: 50-80%

High Grade (HG) AIN: 30-50%

AIN screening?

Treatment of AIN

- Hardly any prospective studies
- Ablation via heat coagulation is the standard treatment option
  - Suboptimal response rates
  - Recurrence rate is high
- Alternative ablative therapies:
  - Trichloroacetic acid (TCA)
  - Liquid nitrogen
- Alternative non-ablative therapies
  - Imiquimod (TLR-9 agonist, IFN-gamma inducer)
  - 5-fluoroacil (cytostatic)

Triple arm trial in 146 HIV+ MSM

- Screening by high resolution anoscopy
- Histopathologically proven AIN
- Randomisation:
  - 16 wks imiquimod 3 times a week
    - patient administered
  - 16 wks topical 5-fluorouracil twice a week
    - patient administered
  - 16 wks of monthly electrocautery (up to 5 sessions)
    - provider administered

Response Rate

	Imiquimod				Fluorouracil				Electrocautery			
	mITT (n=54)	PP (n=45)	PP high-grade AIN (n=24)	PP low-grade AIN (n=21)	mITT (n=48)	PP (n=43)	PP high-grade AIN (n=28)	PP low-grade AIN (n=15)	mITT (n=46)	PP (n=36)	PP high-grade AIN (n=19)	PP low-grade AIN (n=17)
Complete response												
Number of participants	13	13	5	8	8	8	6	2	18	18	10	8
% (95% CI)	24% (15–37)*	29% (18–43)†	21% (9–41)	38% (21–59)	17% (8–30)*	19% (9–33)†	21% (10–40)	13% (2–39)	39% (26–54)*	50% (34–66)†	53% (32–73)	47% (26–69)
Partial response												
Number of participants	6	6	6	NA	6	6	6	NA	3	3	3	NA
% (95% CI)	11% (5–23)	13% (6–27)	25% (12–45)	NA	13% (5–25)	14% (6–28)	21% (10–40)	NA	7% (2–18)	8% (2–23)	16% (5–38)	NA
No response												
Number of participants	26	26	13	13	29	29	16	13	15	15	6	9
% (95% CI)	48% (35–61)	58% (43–71)	54% (35–72)	62% (41–79)	60% (46–73)	67% (52–80)	57% (39–74)	87% (61–98)	33% (21–47)	42% (27–58)	32% (15–54)	53% (31–74)
Excluded												
Number of participants	9	NA	NA	NA	5	NA	NA	NA	10	NA	NA	NA
% (95% CI)	17% (9–29)	NA	NA	NA	10% (4–23)	NA	NA	NA	22% (12–36)	NA	NA	NA

mITT=modified intention to treat. PP=per protocol. AIN=anal intraepithelial neoplasia. NA=not applicable (in case of low-grade AIN partial response is not an option). *Difference between the three groups in complete response rate was significant in the mITT analysis (p=0·027). †Difference between the three groups in complete response rate was significant in the PP analysis (p=0·010).

Table 2: Response rates 4 weeks after the end of treatment

Richel et al 2013 Lancet Oncol

Response for peri-anal and intra-anal lesions separately

	Intra-anal lesions			Peri-anal lesions		
	Imiquimod	Fluorouracil	Electrocautery	Imiquimod	Fluorouracil	Electrocautery
Complete response						
n/N	9/41	7/42	16/34	9/9	4/7	3/4
% (95% CI)	22% (12–37)	17% (8–31)	47% (31–63)	100% (73–100)	57% (25–84)	75% (29–97)
Partial response						
n/N	6/41	7/42	3/34	..	..	..
% (95% CI)	15% (7–29)	17% (8–31)	9% (2–24)	..	..	..
No response						
n/N	26/41	28/42	15/34	0/9	3/7	1/4
% (95% CI)	63% (48–76)	67% (51–79)	44% (29–61)	0% (0–28)	43% (16–75)	25% (3–71)

Assessment of response by localisation. The cumulative number of peri-anal and intra-anal lesions exceeded the total number of patients, because some patients had both peri-anal and intra-anal lesions. For intra-anal lesions, groups differed significantly in complete response (p=0·0080) and overall (complete+partial) response (p=0·045). For peri-anal lesions, groups did not differ significantly in response (p=0·36).

Table 4: Response to treatment (per protocol) for peri-anal and intra-anal lesions separately

Cumulative recurrence

	All patients	Imiquimod	Flurouracil	Electrocautery
24 weeks	22% (11/50)	19% (3/16)	38% (5/13)	14% (3/21)
48 weeks	46% (22/48)	47% (7/15)	50% (6/12)	43% (9/21)
72 weeks	67% (30/45)	71% (10/14)	58% (7/12)	68% (13/19)

Data are % (n/N).Cumulative recurrence rates at weeks 24, 48, and 72 after treatment. Of the 54 patients initially responding to treatment, 50 patients returned for a follow up high resolution anoscopy 24 weeks after treatment. An additional two and three patients were lost to follow up at the 48-week and 72-week visits.

Table 3: **Cumulative recurrence rates**

Richel et al 2013 Lancet Oncol

conclusion

Electrocautery is more effective than imiquimod and 5-FU for the treatment of intra anal AIN, but all have high recurrence rates

Imiquimod seems to be treatment of choice for peri-anal AIN

Electrocautery shows milder and shorter lasting side effects

HGAIN, years on ART and high CD4 count are related to treatment success

- HPV vaccination before the initiation of sexual activity
- 602 healthy MSM
  - 16-26 yrs
  - < 5 sex partners life time
- The rate of high grade AIN related to HPV-6, 11, 16, or 18 was reduced by:
  - 54.2% (95% CI, 18.0 to 75.3) in the intention-to-treat population
  - 74.9% (95% CI, 8.8 to 95.4) in the per-protocol population
- Few boys identify themselves to parents or physicians as MSM by this time.

Quadrivalent HPV Vaccination After Effective Treatment of Anal Intraepithelial Neoplasia in HIV+ Men **(VACCAIN-P)**

- Goldstone et al 2012: open study 202 patients treated for HGAIN
  - 88 vaccinated: 13.6% recurrent HGAIN
  - 114 unvaccinated: 30.7% " "
- Vaccination with quadrivalent HPV vaccine versus placebo on prevention of high grade AIN recurrence in HIV-positive MSM who were successfully treated for high grade AIN.
- Multicenter, randomised, double-blind clinical trial in 4 hospitals in the Netherlands (n=200)
- Primary end point will be the cumulative recurrence of HG AIN at 12 months after the last vaccination, as assessed by HRA (High-Resolution Anoscopy), with biopsies taken of suspect lesions

ZonMw

Therapeutic vaccine using E7 protein as target

- HspE7: fusion of the human papillomavirus (HPV) 16 E7 protein and the Mycobacterium bovis heat shock protein 65
- Phase I/II trial to study the effectiveness of HspE7
- 3 cohorts of 5 participants each, sequentially assigned to receive 100, 500 or 1000 mg HspE7, injected 3 times subcutaneously at 4-week intervals.
- HspE7 was well tolerated, no sign changes in VL or CD4 count
- 3/5 (60%) with disease regression became HPV-negative, compared with none of 10 with no clinical response (P = 0.02)

Palefsky, AIDS 2006

Therapeutic HPV-16 Vaccination for the Treatment of Anal Dysplasia **(VACCAIN-T)**

- Kenter et al NEJM 2009: VIN (vulvar intraepithelial neoplasia) synthetic long-peptide vaccine SLP HPV-01® (peptides from the HPV-16 viral E6 and E7)
  - Well tolerated, effective >70% HGVIN
  - Strong HPV-16-specific immune response
  - Highly efficacious
- Safety/ toxicity of the HPV-16 vaccine in HIV+ MSM
- Regression of intra-anal high grade AIN lesion
- HPV16-specific immunity in blood
  - T-cell assays: i.e. proliferation (LST), cytokine production (IFNg, TNFa, IL-4, IL-5, IL-10, and IL-2) as well as by ELISPOT (IFNg)
- First phase dose-response study, 3 different dosage schedules SLP-HPV-01®, intradermally with a three-week interval, with or without peg IFN-α. Each vaccination n=5.
- The optimal vaccination schedule will be increased to 20 patients by treating an additional 15 patients.

ZonMw

Ablative interventions

- Tolerability, Safety & Efficacy of Argon Plasma Coagulation for AIN in HIV+ Men
  - Phase II, Prospective, Open-label, Pilot Study, n=20
  - Alexandra de Pokomandy, Centre hospitalier de l'Université de Montréal (CHUM), Canada
  - Recruitment closed awaiting results
- The HPV-SAVE Study Team: HPV Screening and Vaccine Evaluation in MSM
  - Ablative therapy involving either infrared coagulation (IRC) or electrocautery (EC)
  - The control arm includes active surveillance with observation alone
  - Irving Salit, University Health Network, Toronto
  - Not yet recruiting
- A Safety and Tolerability of Circumferential Anal Canal Radiofrequency Ablation For Anal Intraepithelial Neoplasia
  - Open label
  - Radiofrequency Ablation circumferential radiofrequency ablation (RFA) to the anal canal
  - Sponsor: Medtronic
  - Ongoing

Efficacy and safety of topical trichloroacetic acid vs. electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive patients (**TECAIN**) – a randomized controlled multicenter non-inferiority trial

85% TCA vs. electrocautery in AIN of all grades (1-3)
sponsored by the German Federal Ministry of Education and Research, beginning: 04/2015
screening: 2800 HIVpatients

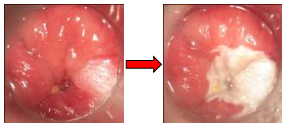
560 patients planned to be included with histologically confirmed AIN

9 study centers in Germany (university hospitals in Essen, Bochum, Dresden, München, and Heidelberg as well as two teaching hospitals in Oberhausen and Köln, and 2 medical practices specialized in HIV in Berlin and Dortmund)

treatment interval: 12 weeks (up to 4 treatments, monthly intervals)

HPV-typing, HPV-DNA-load determination, HPV-oncogene-mRNA

study duration: 36 month, recruitment phase: 18 months



monofocal leucoplacic AIN before and after 85% TCA

Other interventions

- Treatment of Anal HSIL with a Chinese Herbal Topical Cream
  - Placebo controlled
  - Arnebia Indigo Jade Pearl cream 1/4 teaspoon twice daily for 48 weeks.
  - Misha R Cohen, UCSF School of Nursing
  - Awaiting results
- Chemoprevention of AIN in Persons With HIV Infection.
  - To evaluate the effects of isotretinoin alone or in combination with IFN alfa-2a on immune function markers, human papillomavirus (HPV) type, and HPV DNA levels
  - Phase I and II (after ablation)
  - Palefsky JM in collaboration with Hofmann-LaRoche
  - Completed, awaiting results
- CIDOFOVIR 1%, 3 Nights Per Week, During 4 Weeks, of Anal Intraepithelial Neoplasia, High Level, in HIV+ Patients (CIDAN12)
  - Open label
  - Elena Sendagorta, MD Hospital La Paz, Madrid, Spain
  - Completed

Large observational study

- ANCHOR Study: **Anal Cancer**/HSIL Outcomes Research Study
  - Topical or Ablative Treatment in Preventing **Anal Cancer** in Patients With HIV and Anal High-Grade Squamous Intraepithelial Lesions
  - Randomized phase III trial compares topical or ablative treatment with active monitoring in preventing anal cancer in HIV+ patients with high-grade squamous intraepithelial lesions (HSIL).
  - Recruiting (n=5058) expected completion 2022
  - Joel Palefsky, MD AIDS Associated Malignancies Clinical Trials Consortium

Conclusions

- Little evidence based data on the treatment of AIN in HIV+ MSM
  - electrocoagulation is the recommended treatment option
  - urgent need for high quality RCT's
- Most currently available treatment options show disappointing outcome results and high recurrence rates
  - makes screening HIV+ MSM for AIN less effective
- Inducing an effective immune response via **therapeutic** vaccination might be more promising than ablative treatment options
- Universal **prophylactic** HPV vaccination for could eliminate anal cancer on the longer term

AIN in Amsterdam

amc
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