BREACH
BELGIAN RESEARCH AIDS&HIV CONSORTIUM

HPV: results from the Anchor study and implications for clinical practice

Breach Symposium, November 23rd 2022

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Infectious Diseases Department
AIDS Reference Centre

CHU Saint-Pierre
UMC Sint-Pieter

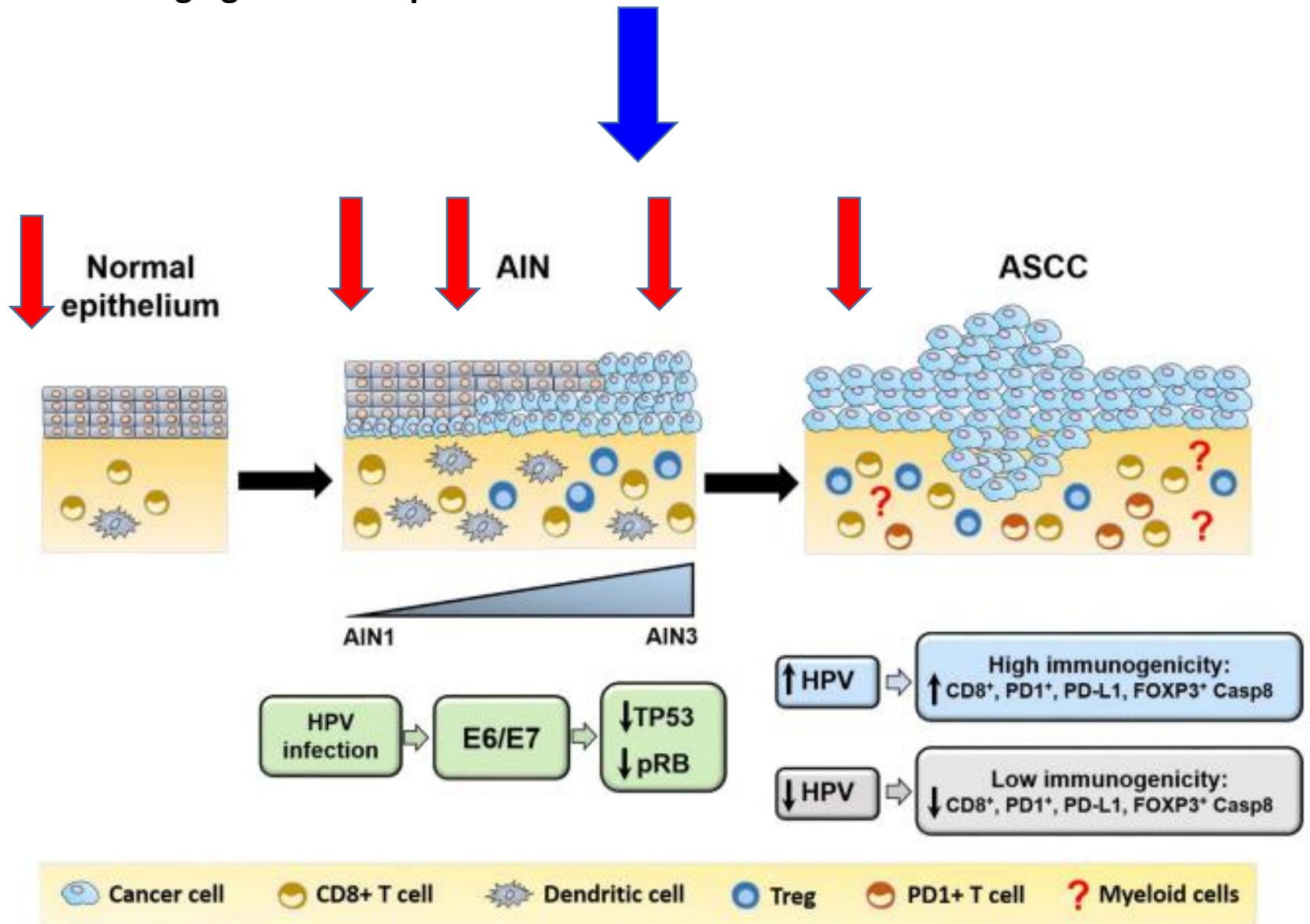
Anal intraepithelial neoplasia

AIN 2 and 3= HSIL
High grade intraepithelial lesions

Adapted from Martin D. Reviews on cancer 2017

Treatment?

Screening



Agenda

- Epidemiology of anal cancer
- Treatment of high-grade lesion HSIL: the Anchor study
- Tools for anal cancer screening
- Other interventions

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- **Epidemiology of anal cancer**
- Treatment of high-grade lesion HSIL: the Anchor study
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Anal Cancer and HIV
High incidence and unfavorable outcome

MSM w HIV
Cohorte D:A:D 2004-2010:
Anal cancer incidence 45-89/100 000 persons year

Worm S. BMC Infect Dis 2013
Clifford G Int J Cancer 2021

HSIL prevalence: 29% (23-35%)
HSIL incidence: 8-15% year

Machalek D. The Lancet 2012

Women wVIH
Anal cancer incidence : 22/ 100 000 persons year
HSIL prevalence (cytology): 12% (8,5-17%) -27%*

Gupta R 2022.HIV med 2012
Clifford G Int J Cancer 2021
*Stier E. CID 2020

Original Article

J Gastrointest Oncol 2019

Treatment outcomes of patients with localized anal squamous cell carcinoma according to HIV infection: systematic review and meta-analysis

Marcos Pedro Guedes Camandaroba[1], Raphael Leonardo Cunha de Araujo[2,3], Virgílio Souza e Silva[1], Celso Abdon Lopes de Mello[1], Rachel P. Riechelmann[1]

Localised anal cancer anal treated with radio- and chemotherapy (1996-2017):

- 40 studies
- 3720 patients: **1.298 (34%) PLHIV** , median CD4 347/µL

PLHIV
More severe skin toxicity grade 3-4
More frequent leukopenia and thrombocytopenia
Higher recurrence rate at 3 years, median 25% [6-67%] **vs 9-33% in** HIV-neg : 1,32 (1,01-1,74; p=0,043)
Lower survival rate at 5 years, median 71% [20-87%] **vs 65-84%** in VIH-neg : 1,39 (1,04-1,85; p=0,024)

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- Epidemiology of anal cancer
- **Treatment of high-grade lesion HSIL: the Anchor study**
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- Other interventions

Treating HSIL in PLHIV

Anchor Study (Anal Cancer/HSIL Outcomes Research)

- National Cancer Institute's Office of HIV and AIDS Malignancy

(Grant number U01 CA121947)

- 2014-2021
- ≥ 35 years PLHIV with biopsy-proven anal HSIL (AIN3 or p16-pos AIN2)
- Phase III, randomized 1/1:

  treatment HSIL (office-based electrocautery ablation)

  vs active monitoring every 6 months (HRA: high resolution anoscopy)
- Primary outcome: Time to progression to anal cancer
- N=4436, 25 sites USA
  - 80% male, 15-16 % female, 3-4% transgender
  - Median age 51 years
  - Median HIV duration: 17 years
- Stratification by
  - lesion size ≤50% vs > 50%
  - CD4: ≤ 200 vs >200/µL

Anchor study

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Treatment Group (N=2227)	Active-Monitoring Group (N=2219)
Median age (IQR) — yr	51 (44–57)	51 (44–57)
Median time since HIV diagnosis (IQR) — yr	17 (10–24)	17 (10–25)
Median follow-up (IQR) — mo	25.3 (11.7–42.0)	27.2 (12.0–42.1)
Gender identity — no. (%)		
Male	1793 (80.5)	1782 (80.3)
Female	346 (15.5)	365 (16.4)
Transgender	85 (3.8)	68 (3.1)
Nonbinary	2 (0.1)	2 (0.1)
Declined to answer	1 (<0.1)	2 (0.1)
Race or ethnic group — no. (%)†		
Black	935 (42.0)	939 (42.3)
Non-Hispanic White	695 (31.2)	737 (33.2)
Non-Black Hispanic	381 (17.1)	339 (15.3)
Asian or Pacific Islander	27 (1.2)	29 (1.3)
Other or unknown	189 (8.5)	175 (7.9)
CDC criterion for risk of HIV infection — no. (%)‡		
Male-to-male sexual contact	1716 (77.1)	1717 (77.4)
Heterosexual	532 (23.9)	510 (23.0)
Injection-drug use	152 (6.8)	177 (8.0)
Transfusion	53 (2.4)	47 (2.1)
Hemophilia	2 (0.1)	4 (0.2)
Other	34 (1.5)	27 (1.2)
Smoking history — no. (%)		
Current smoker	710 (31.9)	743 (33.5)
Smoked >100 cigarettes over lifetime§	1268 (56.9)	1353 (61.0)
History of HSIL treatment ≥6 mo before randomization — no. (%)¶	228 (10.2)	215 (9.7)
Plasma HIV-1 RNA copies/ml — no./total no. (%)		
<50	1853/2213 (83.7)	1800/2201 (81.8)
51–199	155/2213 (7.0)	160/2201 (7.3)
200–1000	83/2213 (3.8)	93/2201 (4.2)
>1000	122/2213 (5.5)	148/2201 (6.7)
Median CD4 count (IQR) — cells/mm³‖	602 (393–827)	607 (410–837)
Nadir CD4 count — no. (%)**		
≤200 cells/mm³	1130 (50.7)	1121 (50.5)
>200 cells/mm³	1097 (49.3)	1098 (49.5)
HSIL size at screening — no. (%)**		
>50% of anal canal or perianal region	285 (12.8)	282 (12.7)
≤50% of anal canal or perianal region	1942 (87.2)	1937 (87.3)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

J.M. Palefsky, J.Y. Lee, N. Jay, S.E. Goldstone, T.M. Darragh, H.A. Dunlevy, I. Rosa-Cunha, A. Arons, J.C. Pugliese, D. Vena, J.A. Sparano, T.J. Wilkin, G. Bucher, E.A. Stier, M. Tirado Gomez, L. Flowers, L.F. Barroso, R.T. Mitsuyasu, S.Y. Lensing, J. Logan, D.M. Aboulafia, J.T. Schouten, J. de la Ossa, R. Levine, J.D. Korman, M. Hagensee, T.M. Atkinson, M.H. Einstein, B.M. Cracchiolo, D. Wiley, G.B. Ellsworth, C. Brickman, and J.M. Berry-Lawhorn, for the ANCHOR Investigators Group*

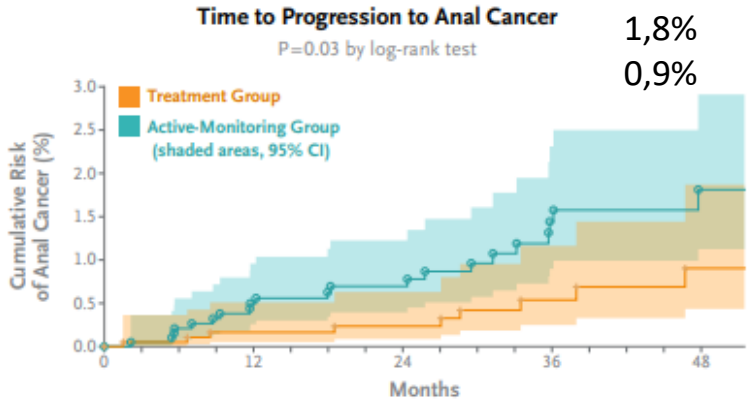
The rate of progression to anal cancer:

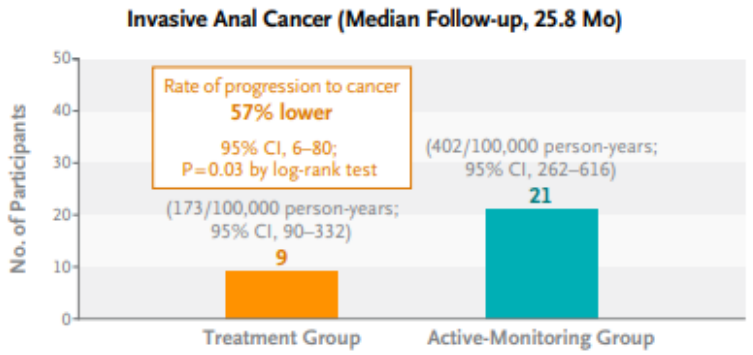
lesion size vs > 50%
1047 per 100,000 person-years

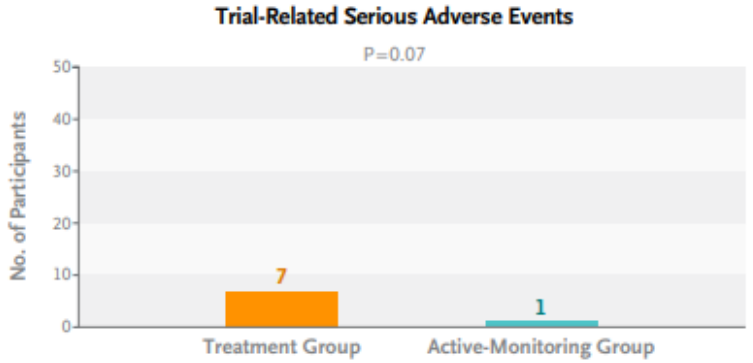
lesion size ≤50%
185 per 100,000 person-years

Number needed to treat 167

48 months:
1,8%
0,9%







Anchor study: questions

1/ Are there **HPV specific genotypes** more associated with evolution to cancer?

2/ Can we use **markers** to detect HSIL associated with progression to cancer?

DNA methylation (marker of HPV-induced carcinogenesis:
multiplex PCR targetting different genes)?

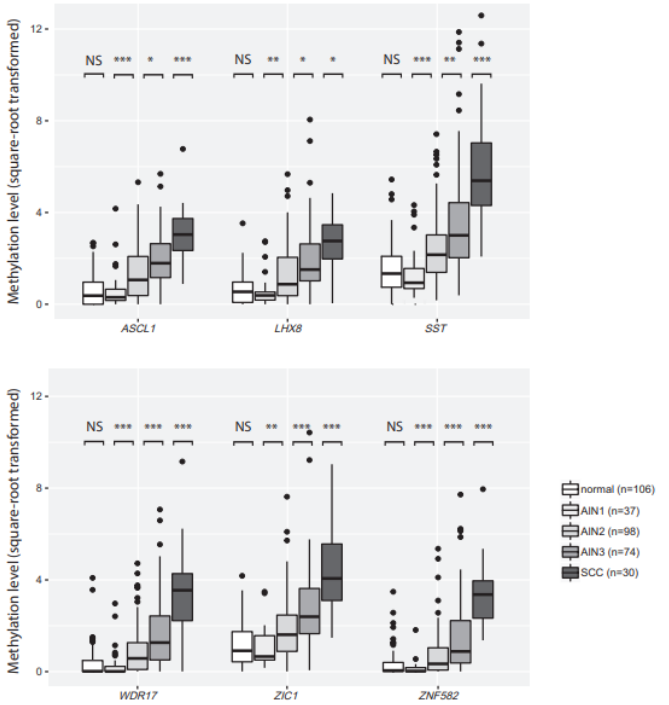


Figure 1. Methylation levels increased with severity of anal disease. DNA methylation levels relative to a reference gene β-actin (square-root transformed ΔΔCq ratios; *y* axis) in the different histological categories of anal tissue samples of HIV-positive men (*x* axis) for 6 markers: *ASCL1, LHX8, SST, WDR17, ZIC1, ZNF582*. Differences between histological categories upon Kruskal-Wallis omnibus test, followed by post hoc testing using the Mann-Whitney *U* test and Bonferroni multiple testing correction: $*P < .05$, $**P < .01$, $***P < .001$. ● outlier sample. Abbreviations: AIN1–AIN3, anal intraepithelial neoplasia (grades 1–3); HIV, human immunodeficiency virus; normal, normal control samples; NS

Clinical Infectious Diseases
MAJOR ARTICLE

Cancer Risk Stratification of Anal Intraepithelial Neoplasia in Human Immunodeficiency Virus–Positive Men by Validated Methylation Markers Associated With Progression to Cancer

Ramon P. van der Zee,[1,2,3] Olivier Richel,[4] Carel J. M. van Noesel,[5] Iuliana Ciocănea-Teodorescu,[6] Annina P. van Splunter,[1] Timo J. ter Braak,[1] Mayura Nathan,[7] Tamzin Cuming,[7] Michael Sheaff,[8] Alexander Kreuter,[9] Chris J. L. M. Meijer,[1] Wim G. V. Quint,[10] Henry J. C. de Vries,[3,11] Jan M. Prins,[2] and Renske D. M. Steenbergen[1,©]

Table 4. Logistic Regression Analysis on Diagnostic Performance for AIN3+ Detection: Multivariable Regression for Optimal Marker Panel (*ZNF582, ASCL1, SST*)

Marker Panel	Non-CV	LOOCV
AUC (95% CI)	.90 (.86–.94)	.89
Sensitivity, %	78	76
Specificity, %	90	90
Missed SCC	0	0

Non–CV, including 95% CI and LOOCV AUCs, are reported. Sensitivity and specificity are for the Youden index threshold. Endpoint: AIN3+ (AIN3 and anal SCC) in anal tissue samples of HIV-positive men.
Abbreviations: AIN3, anal intraepithelial neoplasia (grade 3); AUC, area under the receiver operating characteristic curve; CI, confidence interval; HIV, human immunodeficiency virus; LOOCV, leave-one-out cross-validated; non-CV, non–cross-validated; SCC, anal squamous cell carcinoma.

2021
Longitudinal study with HSIL several years before cancer

Anchor study: questions

3/Treatment of HSIL :
Timing ?
Which treatment: ablation versus excision? Multifocal lesions?

4/Serious AE

Table 2. Adverse Events.

Events	Treatment Group	Active-Monitoring Group
	number	
Adverse events	683	635
Serious adverse events*	586	568
Trial-related adverse events†	43	4
Trial-related serious adverse events‡	7	1
Skin ulceration due to fluorouracil	1	0
Anal abscess due to electrocautery	1	0
Pain due to electrocautery	1	0
Pain due to treatment under anesthesia	1	0
Pain due to infrared coagulation	1	0
Infection or abscess due to anal biopsy	2	1

* Shown are all serious adverse events regardless of intervention, as determined by the investigators. P=0.61 for the between-group difference.
† Shown are adverse events with a possible, probable, or definite relationship to trial interventions, as determined by the investigators.
‡ Shown are serious adverse events with a possible, probable, or definite relationship to trial interventions, as determined by the investigators. P=0.07 for the between-group difference.

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Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

J.M. Palefsky, J.Y. Lee, N. Jay, S.E. Goldstone, T.M. Darragh, H.A. Dunlevy, I. Rosa-Cunha, A. Arons, J.C. Pugliese, D. Vena, J.A. Sparano, T.J. Wilkin, G. Bucher, E.A. Stier, M. Tirado Gomez, L. Flowers, L.F. Barroso, R.T. Mitsuyasu, S.Y. Lensing, J. Logan, D.M. Aboulafia, J.T. Schouten, J. de la Ossa, R. Levine, J.D. Korman, M. Hagensee, T.M. Atkinson, M.H. Einstein, B.M. Cracchiolo, D. Wiley, G.B. Ellsworth, C. Brickman, and J.M. Berry-Lawhorn, for the ANCHOR Investigators Group*

5/How to screen for HSIL?

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- Epidemiology of anal cancer
- Treatment of high-grade lesion HSIL: the Anchor study
- **Tools for anal cancer screening**
- Other interventions

Tools for anal cancer and HSIL screening

- Screening for HSIL: precursor of anal cancer
- Screening cancer itself

Anal cancer survival rate when diagnosed	
≤ 2cm	80%
≤ 1cm	100%

- Asking for symptoms: pain, bleeding, local mechanical symptoms, …
- DARE digital ano-rectal examination
- Anal swab
  - Cytology
  - HPV DNA
  - Other markers of cellular proliferation (p16/Ki67, E6/E7 mRNA,…)
- High resolution anoscopy (HRA)

Asking for symptoms

Sauter *et al. BMC Gastroenterology* (2016) 16:46
DOI 10.1186/s12876-016-0461-0

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Presenting symptoms predict local staging of anal cancer: a retrospective analysis of 86 patients

Matthias Sauter[1,2†], Georg Keilholz[3†], Helmut Kranzbühler[3], Norbert Lombriser[3], Meher Prakash[2], Stephan R. Vavricka[2,4] and Benjamin Misselwitz[2*]

HSIL:
most anal symptoms are not a useful marker of anal HSIL

Table 2 Clinical symptoms of patients with various tumor stages (expressed as percent of total number of patients with respective tumor stage). Statistical analysis: Generalized linear model

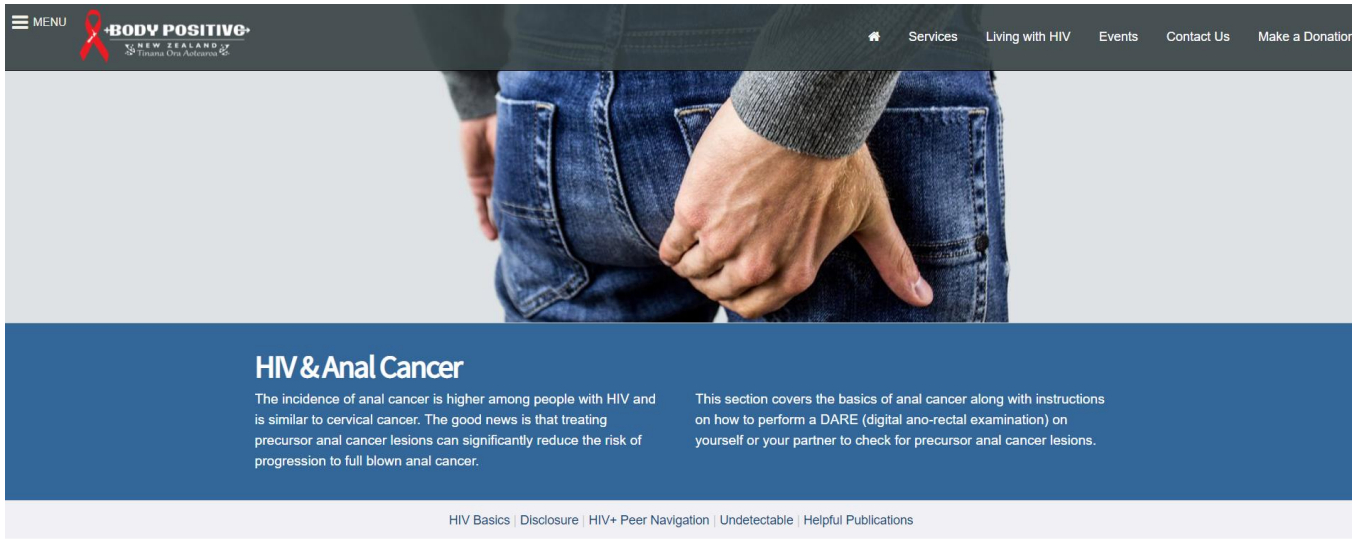
		All	T1	T2	T3	T4	χ^2
		$n = 86$	$n = 8$	$n = 32$	$n = 25$	$n = 21$	significance
Blood in stool		78 %	75 %	77 %	84 %	76 %	0.78
Pain	Painful defecation	38 %	25 %	26 %	52 %	48 %	0.26
	Anal pain	29 %	25 %	29 %	24 %	33 %	0.83
	Perianal pain	24 %	0	10 %	32 %	48 %	<0.01
Defecation and stool irregularities	Outlet obstruction	7 %	0	3 %	12 %	10 %	0.20
	Incontinence	12 %	0	6 %	16 %	19 %	0.07
	Pencil stool	6 %	0	6 %	4 %	10 %	0.45
	Diarrhea	11 %	0	10 %	16 %	10 %	0.50
	Irregular stool	7 %	0	6 %	8 %	10 %	0.40
	Constipation	6 %	0	0	8 %	14 %	0.02
Local mechanical symptoms	Foreign body sensation	22 %	0	2 %	20 %	29 %	0.28
	Pruritus	21 %	37 %	29 %	16 %	5 %	<0.01
	Tumor on self-palpation	26 %	25 %	26 %	24 %	29 %	0.81
Other organ involvement	Abdominal pain	5 %	0	0	4 %	14 %	0.02
	Mechanical ileus	1 %	0	0	0	5 %	0.16
	Vaginal stool	1 %	0	0	0	5 %	0.16
	Inguinal lymph nodes on self-palpation	2 %	0	3 %	0	5 %	0.64
Systemic symptoms/findings	Weight loss	31 %	25 %	20 %	30 %	60 %	<0.01
	Anemia	2 %	0	0	4 %	5 %	0.22
Asymptomatic		1 %	12 %	0	0	0	0.63
Total symptoms		3.3	2.12	2.75	3.52	4.43	<0.01

DARE digital ano-rectal examination

- Self DARE: Patients taught to self DARE were able to find lesions of ≥ 3 mm (sens. 71-80%, specificity 92-100%)

  Nyitray et al. Sex Transm Infect 2018

- Australia : Ong et al. J Intern AIDS Society 2018
  - 327 MSM LwHIV followed for 2 years with annual DARE
  - Baseline: 26% had abnormalities, 5% refered to colo-rectal surgeon, anal cancer=1
  - Year 1: 19%, 1%
  - Year 2: 17%, 5%
  - Good acceptability for both patients and physicians
  - Rare adverse outcome (pain, bleeding)



https://www.bodypositive.org.nz/Pages/HIV_and_AnalCancer/#DARE

Quicklinks:

- Anal Cancer
- Preventing HPV and anal cancer
- Who is at risk?
- Anal cancer in people living with HIV
- Symptoms
- Treatment and management
- Digital Ano-Rectal Examination (DARE)
- Why should I have a DARE?
- Performing a DARE
- If you're concerned about anal cancer

Screening for anal cancer precursor HSIL

	Sensitivity	Specificity	NPV
Cytology	61-93%	32-67%	87%
High risk HPV DNA primary testing			
MSM LHIV	96-100%	28%	>90%
W LHIV	**83%**	**61-67% (vs 50 for cytology)**	

Screening strategies for the detection of anal high-grade squamous intraepithelial lesions in women living with HIV

Elizabeth Y. Chiao[a], Shelly Y. Lensing[b], Dorothy J. Wiley[c], Ashish A. Deshmukh[d], Jeannette Lee[b], Teresa M. Darragh[e], Mark H. Einstein[f], Naomi Jay[g], John Michael Berry-Lawhorn[g,h], Joel M. Palefsky[g,i], Timothy Wilkin[j], Luis F. Barroso[k], Ross D. Cranston[l], Rebecca Levine[m], Humberto M. Guiot[n,o], Audrey L. French[p], Deborah Citron[q], Masoumeh Katayoon Rezaei[r], Stephen E. Goldstone[s] and Elizabeth A. Stier[t]

AIDS 2020

Screening for anal cancer precursor HSIL

The Journal of Infectious Diseases
MAJOR ARTICLE
2021

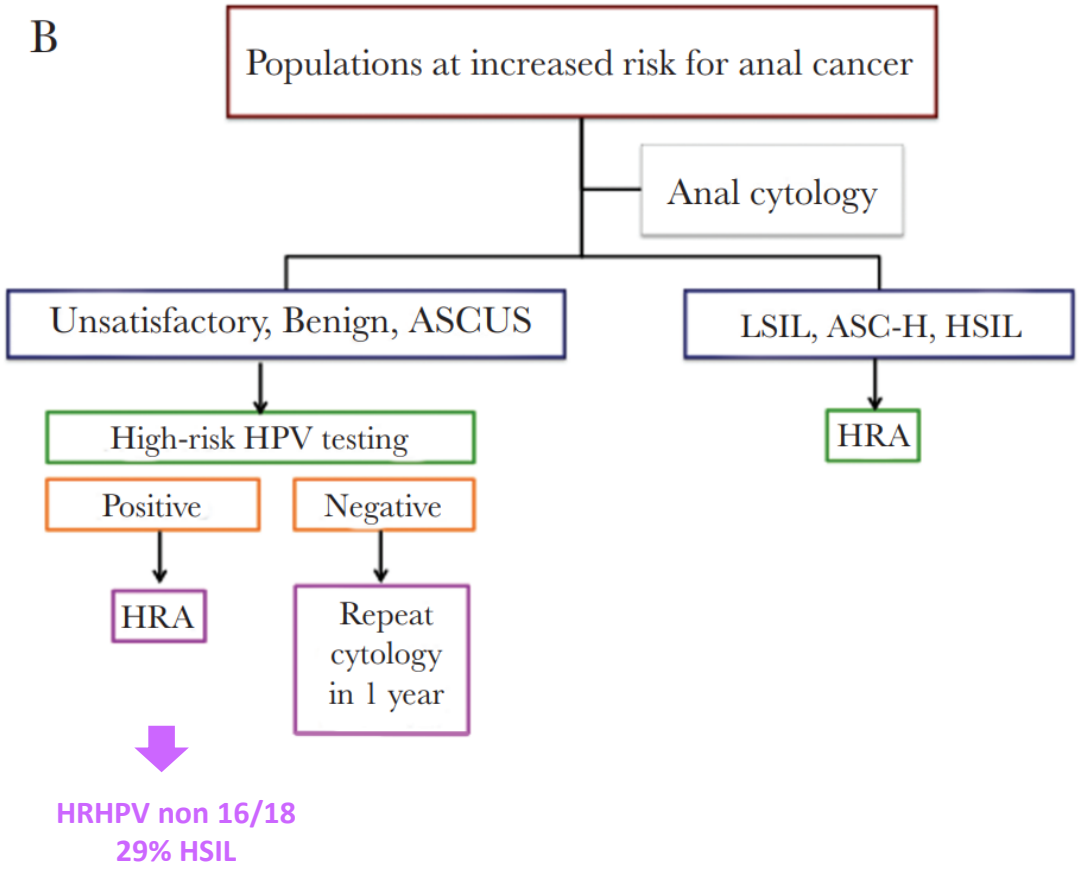
Comparing Anal Cancer Screening Algorithms Using Cytology and Human Papillomavirus DNA Testing in 3 High-Risk Populations

Michael M. Gaisa,[1] Keith M. Sigel,[2] Ashish A. Deshmukh,[3] Volha Lenskaya,[4] Courtney A. Chan,[1] Richard Silvera,[1] John Winters,[1] and Yuxin Liu[4]

[1]Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA, [2]Division of General Internal Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA, [3]Department of Management, Policy and Community Health, University of Texas School of Public Health, Houston, Texas, USA, and [4]Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

- N= 1837
  - 1504 MSM wHIV,
  - 155 MSM without HIV
  - 178 women wHIV
- 41% HSIL

- Co-testing cytology and HPV



Tools for anal cancer screening

- **High resolution anoscopy (HRA)**

- Need well-trained physician
  - At least 50 HRA/year
  - At least 20 HSIL/year
- Timely? < 15 minutes?
- Costly
- Not always reimbursed
  - Rectoscopy+biopsy: 75 euros/40 reimbursed
- May cause pain, bleeding and infection
- How to prioritize patients?

(*J Low Genit Tract Dis* 2016;20: 283–291)

CONSENSUS TERMINOLOGY

2016 IANS International Guidelines for Practice Standards in the Detection of Anal Cancer Precursors

Richard John Hillman, MD, PhD,[1,2] Tamzin Cuming, MD,[3] Teresa Darragh, MD,[4] Mayura Nathan, MBBS, FRCP,[5] Michael Berry-Lawthorn, MD,[6] Stephen Goldstone, MD,[7] Carmella Law, MB, BS, FAChSHM, MBA,[8] Joel Palefsky, MD,[9] Luis F. Barroso, MD,[10] Elizabeth A. Stier, MD,[11] Céline Bouchard, MD,[12] Justine Almada, BA,[13] and Naomi Jay, PhD, RN[14]

Received: 7 April 2020 | Revised: 11 June 2020 | Accepted: 17 June 2020
DOI: 10.1002/ijc.33185

CANCER EPIDEMIOLOGY

A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale

Gary M. Clifford[1] | Damien Georges[1] | Meredith S. Shiels[2] | Eric A. Engels[2] | Andreia Albuquerque[3,4] | Isobel Mary Poynten[5] | Alexandra de Pokomandy[6] | Alexandra M. Easson[7] | Elizabeth A. Stier[8]

General population
Incidence of anal cancer: 1-2/100 000 person-year

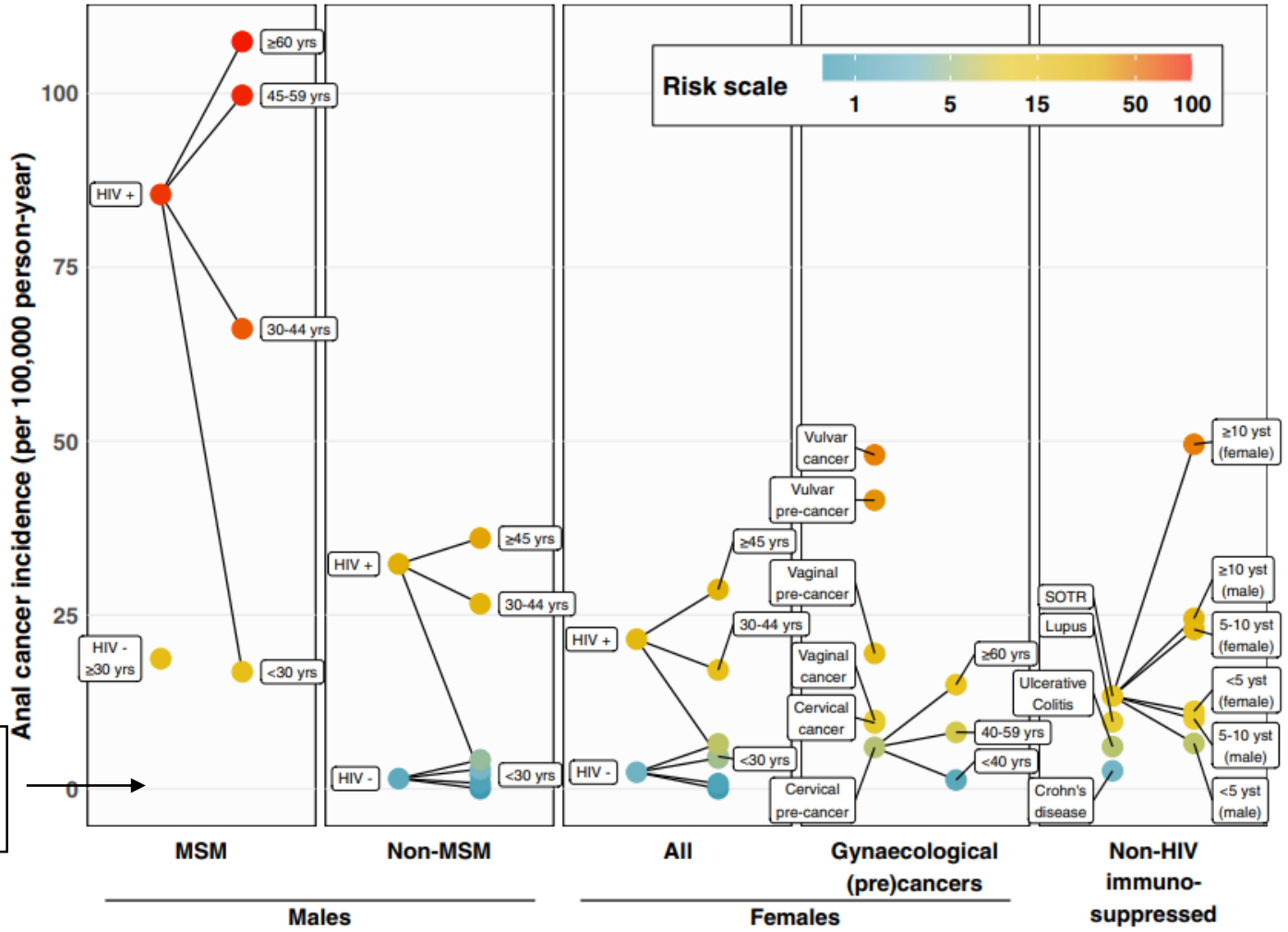
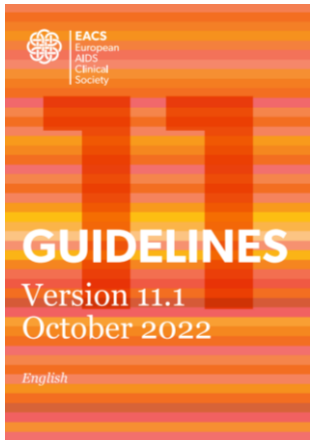


FIGURE 5 Anal cancer risk scale. 95% CIs around the point estimates can be found in the relevant Figures 1-4 and Tables S1 and S2. Estimates for HIV-negative men and men are shown, without labels, for age-groups <30, 30 to 44, 45 to 59, and ≥60 years (see Section 3). CI, confidence interval; MSM, men who have sex with men; MSW, men who have sex with women. yrs, years old; yst, years since transplant

Recommendations and guidelines



Cancer: Screening Methods[I]

Problem	Persons	Procedure	Evidence of benefit	Screening interval	Additional comments
Anal cancer	MSM and persons with HPV-associated dysplasia[IX]	Digital rectal exam ± anal cytology	Unknown; advocated by some experts	1-3 years	If anal cytology abnormal, anoscopy
Breast cancer	Women 50-70 years	Mammography	↓ Breast cancer mortality	1-3 years	
Cervical cancer	HIV-positive women > 21 years	PAP smear or liquid based cervical cytology test	↓ Cervical cancer mortality	1-3 years	HPV genotype testing may aid PAP/liquid based cervical screening

BHIVA	?
USA	NIH (https://clinicalinfo.hiv.gov/) No age recommendation, Anchor study is ongoing
Australia	Annual DARE for men ≥ 50 years-old (since 2016, cost effectiveness study)
French	Guidelines but no age recommendation

Agenda

- Epidemiology of anal cancer
- Treatment of high-grade lesion HSIL: the Anchor study
- Tools for anal cancer screening
- **Other interventions**

Other interventions

1. Continue surveillance: recurrence 40-70%

2. Stop smoking

3. Vaccination against HPV

4. Maintain sustained HIV viral load undetectability

Smoking increases HPV-induced lesions:
Promote smoking cessation

- Several **case-control studies** show statistically significant greater risk of HPV-induced lesions in smokers, especially current smokers

Anal cancer

- RR 1.9 for 20 pack-years — Holly EA et al. J Natl Cancer Inst. 1989 (USA)
- RR 5.2 for 50 pack-years
- OR = 2.59, (95% CI: 1.25, 5.34) — Swiss HIV Cohort Study. Bertisch B et al. Am J Epidemiol. 2013

Anal HSIL

Current smokers (OR: 1.71, 95% CI: 1.04–2.82) compared to non-smokers

after adjusting for age, sexual risk group, lifetime number of sexual partners, HIV status, and HR-HPV infection.

Keller et al. Cancer Treatment and Research Communications 2022

Smoking increases HPV-induced lesions:
promote smoking cessation

Cancer Epidemiology 68 (2020) 101793

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

2020

Exposure to tobacco smoke measured by urinary nicotine metabolites increases risk of p16/Ki-67 co-expression and high-grade cervical neoplasia in HPV positive women: A two year prospective study

Christine M. White[a,b,*], Salih Bakhiet[b], Mark Bates[a,b], Carmel Ruttle[b], Loretto J. Pilkington[b], Helen Keegan[b], Sharon A. O'Toole[c], Linda Sharp[d], Ruth O'Kelly[b], Prerna Tewari[a,b], Grainne Flannelly[e], Cara M. Martin[a,b,1], John J. O'Leary[a,b,1], On behalf of the CERVIVA consortium

Why smoking could increase HPV-induced lesions?

- Tobacco compounds are found in cervical mucus: inducing genomic damage?
- Smoking reduce Langerhans cells in the cervix

- **Prospective longitudinal study** in Dublin
- LSIL or ASCUS HPV pos (n=275)
- Colposcopy during 2 years
- Measure
  - Tobacco exposure by urine measures of nicotine metabolites
  - Co-expression of p16/Ki67 by immunocytochemistry on cervical smears (markors of HPV transformed cells undergoing proliferation)
- HPV positive women exposed to tobacco smoke are at a higher risk of testing positive for p16/Ki-67co-expression.
- Risk of HSIL(CIN2+) is almost doubled in women who are exposed to tobacco smoke

Vaccination against HPV after HSIL treatment as secondary prevention against HSIL recurrence

21,059 women
- 3,939 vaccinated
- 17,150 unvaccinated

Significant decrease of new HSIL after vaccination HPV
RR 0.41; 95% CI [0.27; 0.64]

- Post hoc
- Retrospective
- Non randomized
- Based on patient's choice (linked to vaccine cost)

Vaccine 38 (2020) 6402–6409

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Prophylactic HPV vaccination after conization: A systematic review and *meta*-analysis

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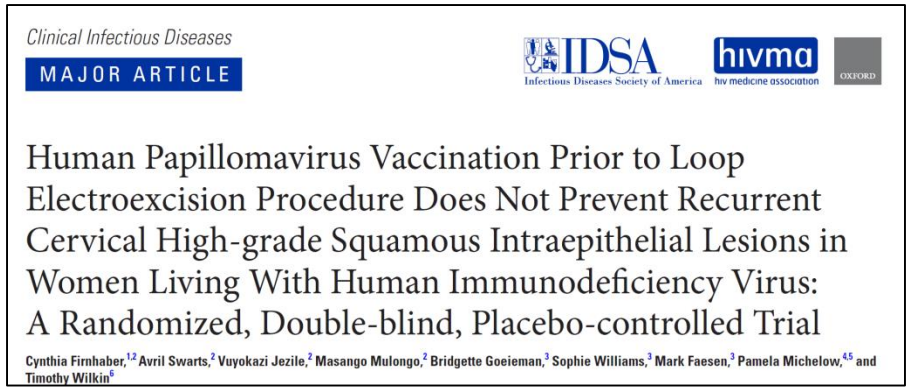
Table 1
Included studies (n.a. = not available).

Reference	Endpoint	Vaccine type	No. of recurrent CIN cases		Risk reduction (%) [95% CI] or study results as reported	Study population	Study design
			Vaccinated cohort 2/4v vaccine n/N (%)	Control group n/N (%)			
Joura et al.	**CIN2+ (HPV-type independent)**	Quadri-valent	**8/474 (1.7)**	**26/592 (4.4)**	**64.9 [20.1–86.3]**	Age 15–26 years Vaccination before surgery	Post-hoc-analysis (FUTURE I and II) Follow-up 2.5 years (median) retrospectively
	CIN2+ (HPV 16, 18)	Quadri-valent	1/474 (0.2)	3/592 (0.51)	61.3 [−382.4 to 99.3]		
Garland et al.	**CIN2+ (HPV-type independent)**	Bivalent	**1/190 (0.53)**	**9/264 (3.41)**	**88.2 [14.8–99.7]**	Age 15–25 years Vaccination before surgery	Post-hoc analysis PATRICIA prospective randomization Follow-up 4 years
	CIN 2+ (HPV 16, 18)	Bivalent	0/190 (0)	4/265 (1.51)	100 (−63.1–100)		
Kang et al.	**CIN2+ (HPV-type independent)**	Quadri-valent	**9/360 (2.5)**	**27/377 (7.2)**	**65.1 (p < 0.05)**	Age 20–45 years Vaccination after surgery	Retrospective Follow-up 3.5 years (median)
	CIN2+ (HPV16, 18)	Quadri-valent	5/197 (2.5)	18/211 (8.5)	70.2 (p < 0.01)		
Ghelardi et al.	**CIN2+ (HPV-type independent)**	Quadri-valent	**2/172 (1.2)**	**11/172 (6.4)**	**81.2 [34.3–95.7]**	Age 18–45 years Vaccination after surgery	Prospective, non-randomized Follow-up 36 years (median)
Hildesheim et al.	**CIN2+ (HPV-type independent)**	Bivalent	**3/142 (2.11)**	**2/169 (1.18)**	**"No significant effect"**	Age 18–25 years Vaccination after surgery	Randomized double blind clinical trial of 7466 Costa Rican women (NCI) Follow-up 57 mo. (HPV +), 27 mo. (LEEP)
	CIN 2+ (HPV 16,18)	Bivalent	**3/142 (2.11)**	**1/169 (0.59)**	**n.a.**		
Pieralli et al.	**CIN 2+ (HPV-type independent)**	Quadri-valent	**0/89 (0)**	**4/89 (4.49)**	**n.a. for CIN 2+**	Age < 45 years Vaccination after surgery	Prospective, randomized Not blinded Follow-up 3 years
	LSIL	Quadri-valent	3/89 (3.37)	8/89 (8.99)	3.4% vs. 13.5% Recurrence (p = 0.0147) NNT 10 HR 0.86 [0.67–1.09]		
Sand et al.	**CIN 2+ (HPV type independent)**	Bi-/Quadri-valent	**82/2074 (3.95)** 14/399 (3.51) (before LEEP) 68/1675 (4.06) (after LEEP)	**777/15054 (5.16)**		Age 17–51 years Vaccination before (0–3 months) or after (0–12 months) surgery	Prospective, cohort study (nationwide registry)
Petrillo et al.	**CIN 2+ (HPV independent)**	Bi-/Quadri-valent	**6/182 (3.29)**	**14/182 (7.69)**	**3.3% vacc vs. 13.6% non-vacc = HR 0.24**	Age 32–47 Vaccination after (0–1 month) after surgery	Retrospective Follow-up 2 years
	CIN 1+	Bi-/Quadri-valent	13/182 (7.14)	17/103 (16.50)	7.1% vacc vs. 16.5% non-vacc = HR 0.43		
Ortega-Quinonero et al.	**CIN 2+ (HPV independent)**	Bi-/Quadri-valent	**5/103 (4.85)**	**22/139 (15.83)**	**4.8% vacc vs. 15.8% non vacc = HR 0.3**	Age 18–65 Vaccination before or after (0–1 month) surgery	Retrospective Follow-up 2 years
	CIN 2 + (HPV 16,18)	Bi-/Quadri-valent	3/51 (5.88)	15/69 (21.74)	5.8% vacc vs. 21.7% non vacc = HR 0.27		
Del Pino et al.	**CIN 2+ (HPV independent)**	Bi-/Quadri-valent	**5/153 (3.27)**	**12/112 (10.71)**	**3.3% vacc vs. 10.7% non vacc = HR 0.31**	Age 26–64 Vaccination after (0–12 months) surgery	Prospective Follow up 22.4 months median

Vaccination against HPV after HSIL treatment as secondary prevention against HSIL recurrence



Clinical Infectious Diseases

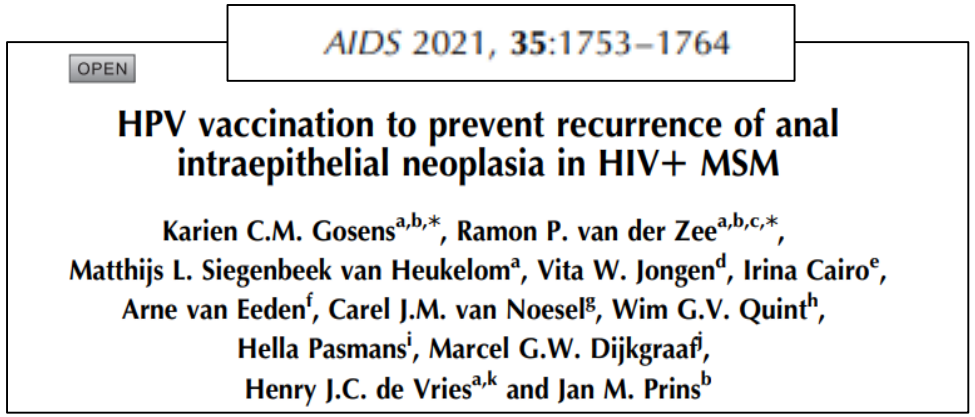
MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Human Papillomavirus Vaccination Prior to Loop Electroexcision Procedure Does Not Prevent Recurrent Cervical High-grade Squamous Intraepithelial Lesions in Women Living With Human Immunodeficiency Virus: A Randomized, Double-blind, Placebo-controlled Trial

Cynthia Firnhaber,[1,2] Avril Swarts,[2] Vuyokazi Jezile,[2] Masango Mulongo,[2] Bridgette Goeieman,[3] Sophie Williams,[3] Mark Faesen,[3] Pamela Michelow,[4,5] and Timothy Wilkin[6]

2021 South Africa
Randomized, double blinded, placebo-controlled
HPV4v, FU 1 years
n= 174, median age 39 years
CD4 489, nadir 116 /µL, HIVRNA <50 cp/ml in 93%
No decrease in recurrence rate
BUT no data on HPV genotypes



AIDS 2021, **35**:1753–1764

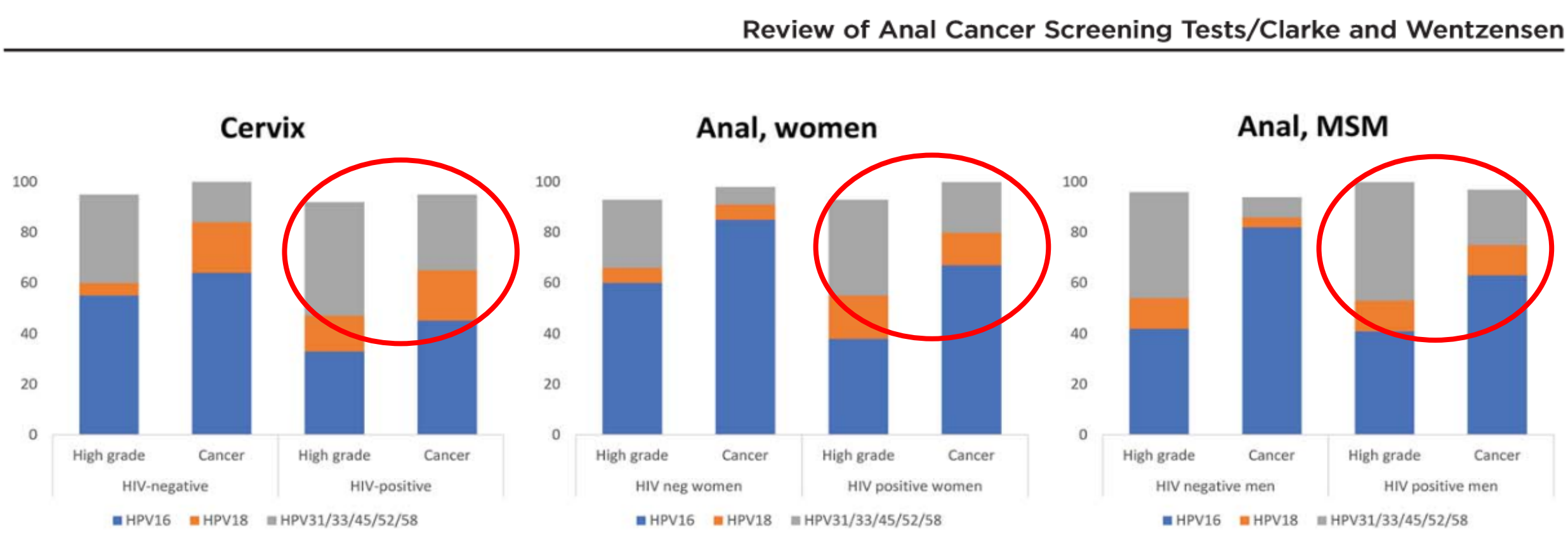
OPEN

HPV vaccination to prevent recurrence of anal intraepithelial neoplasia in HIV+ MSM

Karien C.M. Gosens[a,b,*], Ramon P. van der Zee[a,b,c,*], Matthijs L. Siegenbeek van Heukelom[a], Vita W. Jongen[d], Irina Cairo[e], Arne van Eeden[f], Carel J.M. van Noesel[g], Wim G.V. Quint[h], Hella Pasmans[i], Marcel G.W. Dijkgraaf[j], Henry J.C. de Vries[a,k] and Jan M. Prins[b]

2021 Netherlands NCT02087384
Randomized, double blinded, placebo-controlled
HPV4v, FU untill 12 months after vaccination
N=126, median age 49 years
CD4 700/µL, nadir 240 /µL
HIVRNA <50 cp/ml in 95%
No decrease in recurrence rate
BUT 60% of recurrence caused by non vaccinal HPV genotypes

Which HPV genotypes in PvVIH?



Vaccination against HPV as secondary prevention against HSIL recurrence

Randomized-controlled studies with HPV-9v vaccine or placebo:

Laar *et al. BMC Cancer* (2020) 20:539
https://doi.org/10.1186/s12885-020-07025-7

BMC Cancer

STUDY PROTOCOL Open Access

Adjuvant VACcination against HPV in surgical treatment of Cervical Intra-epithelial Neoplasia (VACCIN study) a study protocol for a randomised controlled trial

R. L. O. van de Laar[1*], W. Hofhuis[2], R. G. Duijnhoven[3], S. Polinder[4], W. J. G. Melchers[5], F. J. van Kemenade[6], R. L. M. Bekkers[7,8] and H. J. Van Beekhuizen[1]

JAMA Network Open

Original Investigation | Infectious Diseases

Effect of Human Papillomavirus Vaccine to Interrupt Recurrence of Vulvar and Anal Neoplasia (VIVA)
A Trial Protocol

Helen C. Stankiewicz Karita, MD; Kirsten Hauge, MPH; Amalia Magaret, PhD; Constance Mao, MD; Jeffrey Schouten, MD, JD; Verena Grieco, MD; Long Fu Xi, PhD; Denise A. Galloway, PhD; Margaret M. Madeleine, PhD; Anna Wald, MD, MPH

NCT03051516
2017-2022
USA
HIV+ and - subjects included

Antiretroviral therapy against HIV significantly decreases HPV-infection and induced lesions in WLwHIV

Association of antiretroviral therapy with high-risk human papillomavirus, cervical intraepithelial neoplasia, and invasive cervical cancer in women living with HIV: a systematic review and meta-analysis

*Helen Kelly, Helen A Weiss, Yolanda Benavente, Silvia de Sanjose, Philippe Mayaud, for the ART and HPV Review Group**

17 studies on ART impact on cervical lesions (longitudinal).

After adjustment for CD4 and treatment duration, cART is associated with

Lower risk

-**HSIL-CIN2+ incidence** 1830 WwVIH (0.59, 0.40–0.87; I^2=0%)

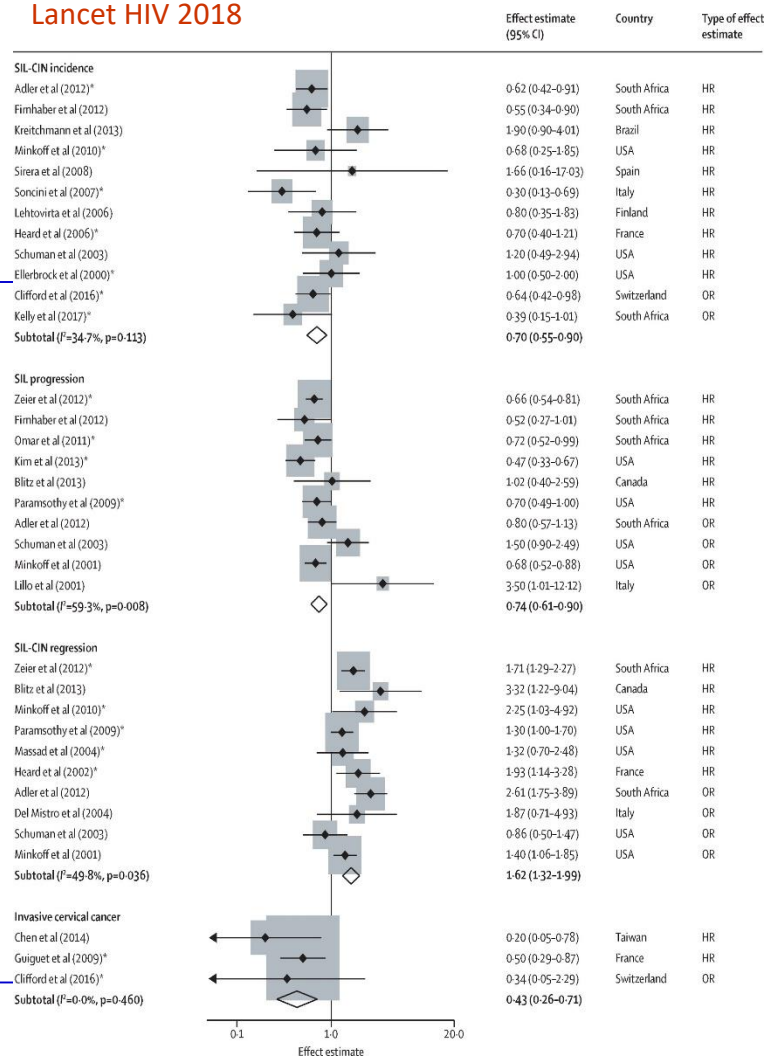
-**SIL progression** 6212 WwVIH (aHR 0.64, 95% CI 0.54–0.75)

-Cervical cancer incidence 15 846 WwVIH (HR 0.40, 95% CI 0.18–0.87).

Increased regression of

-**SIL or CIN** 5261 WwVIH (1.54, 1.30–1.82).

Lancet HIV 2018



Antiretroviral therapy against HIV significantly decreases HPV-infection and induced lesions in MLwHIV

Longitudinal study n=247 MSM on cART since 22 months, FU 61 months
de Pokomandy. *CID 2011.*

Patients with cART >4 years have decreased risk of HGAIN (OR=0.28; 95%CI:0.07-1.06)

Cross-sectional study n=250 MSM, CD4 490, nadir 229, 80% cART since 7 years
Van der Snoeck E. *Sex transm Dis 2012.*

Decreased HPV and AIN if cART

Cohort, n= 311 , 89% under cART (median =9 years)
Richel O. *PLoSOne* 2013

Inverse correlation between duration of cART and AIN (-8%/year)

American veterans cohort: retrospective analysis, n= 45.000, 377 with anal cancer, 1985-2009
Chiao E. *J Acquir Immune Def Syndr* 2013.

Anal cancer decreases if HIVRNA is undetectable >60% of time vs <20% (odds ratio, 0.56; P = 0.040)

Retrospective study n=1654 preHAART (<1996) & postHAART (1996-2008).
Duncan K. *AIDS* 2015

Time to anal cancer shorter if treated before HAART-era (AHR=3.04 (1.48-6.24), p=.002) suggesting that HAART slows down progression from AINHG to cancer

Cross-sectional study n=320 MSM, cART since 5 years
Libois A. *Sex Transm Infect 2016*

Patients with cART≥ 2 years had decreased risk of HSIL (OR=0.32; 95%CI:0.16-10.63)

Conclusion

- Anal cancer is frequent in PLHIV and has a less favorable outcome than in the general population

- Screening of cancer and its precursor (HSIL) should be proposed with
  - Systematic research of symptoms
  - Annual DARE
  - Cytology for men and women
  - HPV DNA for women
  - Referral to High Risk Anoscopy

- Treatment of HSIL significantly reduces the incidence of cancer
- Therapy for HSIL should be improved

- Smoking cessation and maintaining HIV suppression on the long term should also be promoted

- Vaccination against HPV seems to reduce HSIL recurrence after treatment and is currently under investigation