

Treatment of High-Grade Anal Dysplasia

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Fundació Lluita contra la Sida

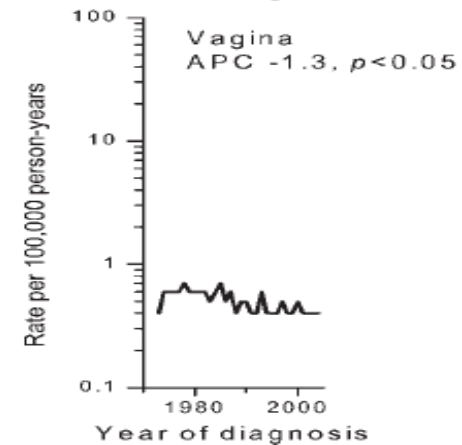
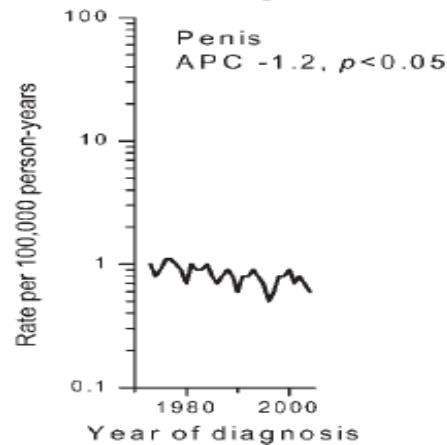
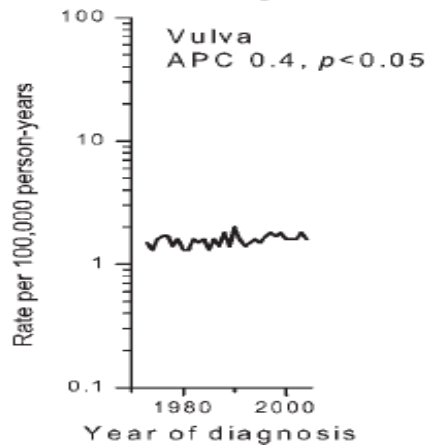
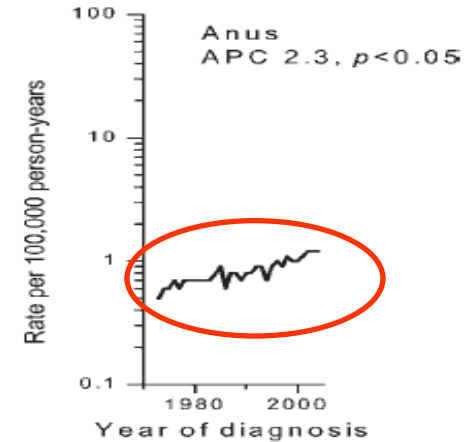
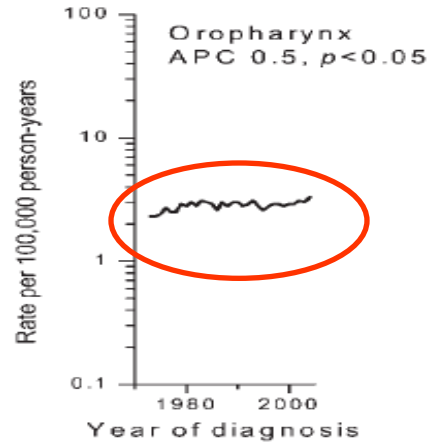
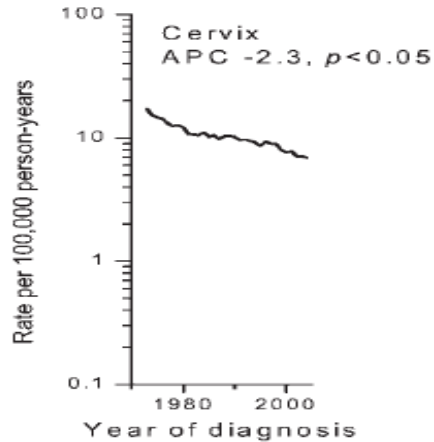
Context

- What is the problem?
- What are we doing about it?
- What do we need to do better?

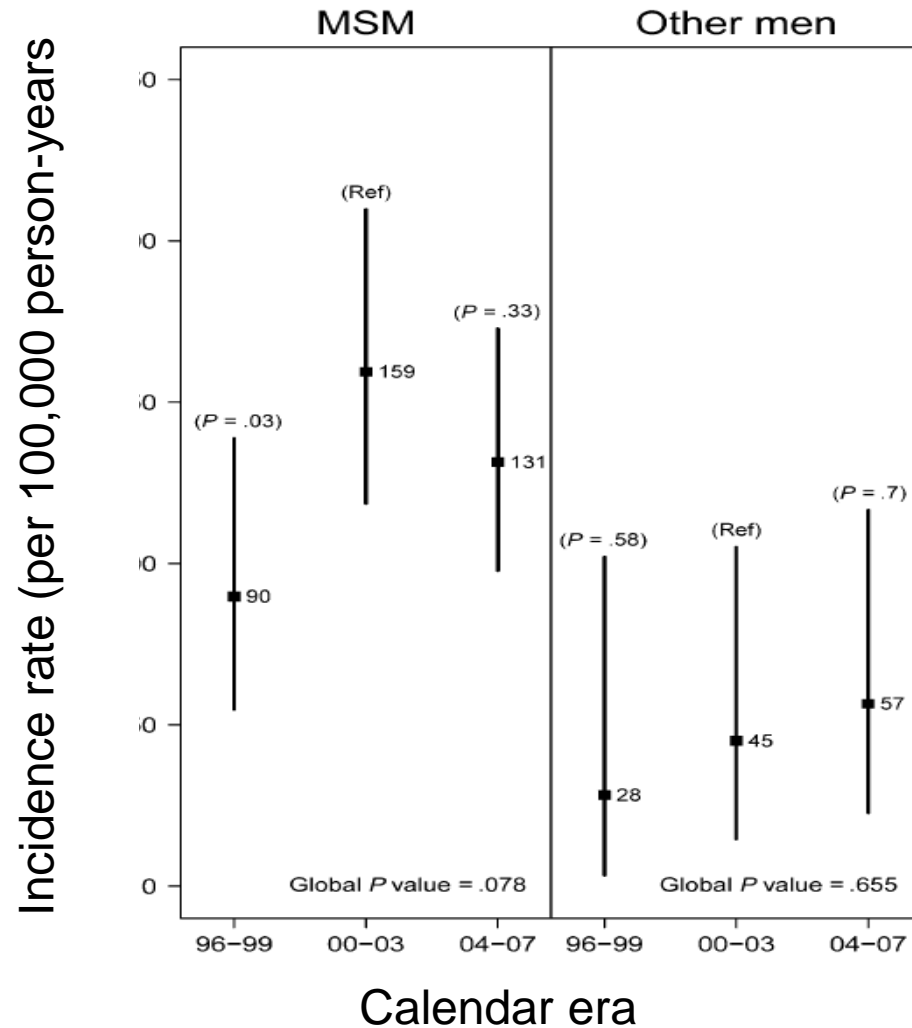


**KEEP
CALM
AND
EVALUATE**

HPV Associated Cancers



Anal Cancer Incidence and HIV

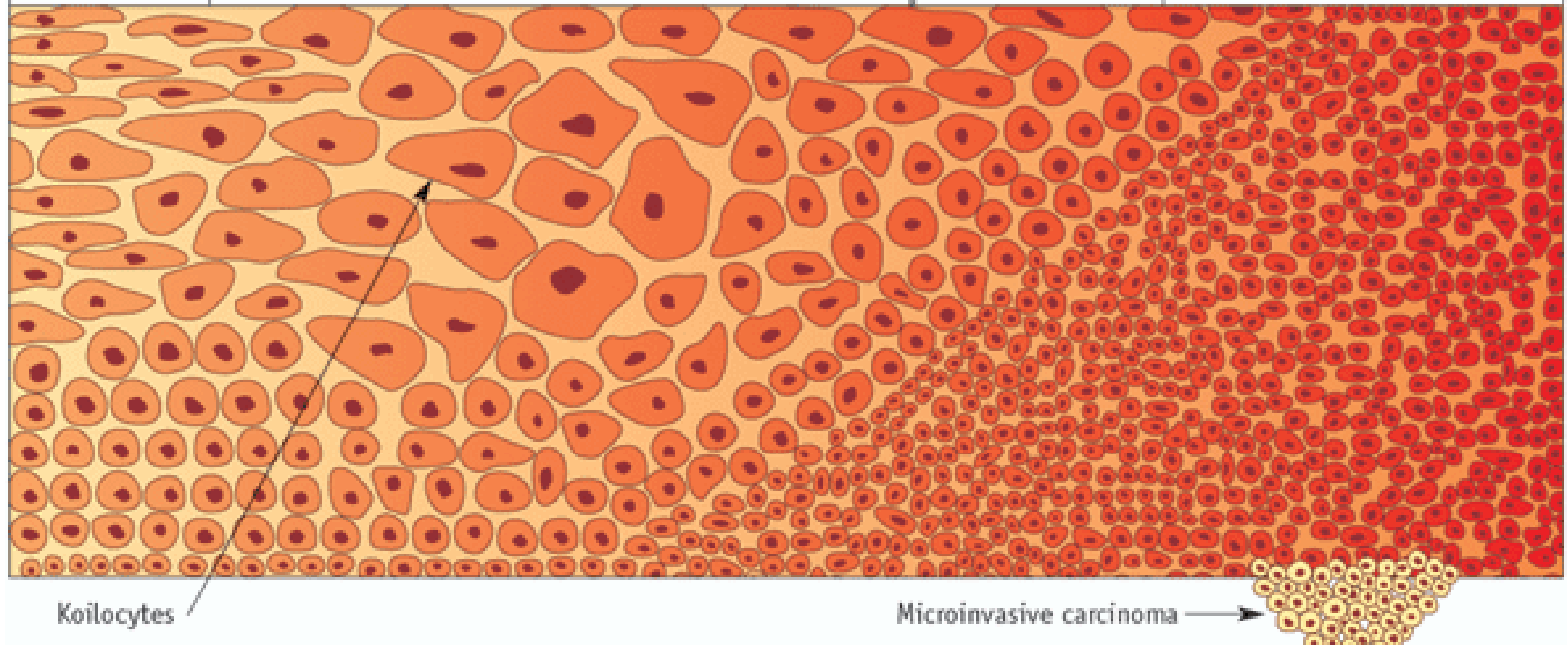


Anal Cancer Survival

Stage distribution and 5-year relative survival by stage at diagnosis for 1999-2006, all races, both sexes

Stage at Diagnosis	Stage distribution (%)	5-year relative survival (%)
Localized (confined to primary site)	50	80.1
Regional (spread to regional LN)	29	59.8
Distant (cancer has metastasized)	12	30.5
Unknown (unstaged)	9	56.0

Figure 1. Schematic Representation of SIL	Low-grade squamous intraepithelial lesion (LSIL)		High-grade squamous intraepithelial lesion (HSIL)	
	Condyloma	CIN/AIN grade 1	CIN/AIN grade 2	CIN/AIN grade 3
Normal	Very mild to mild dysplasia		Moderate dysplasia	Severe dysplasia / <i>In situ</i> carcinoma



As shown in this illustration, with increasing severity of SIL, of either the cervix or anus, the proportion of the epithelium replaced by immature cells with large nuclear-cytoplasmic ratios increases. Invasive cancer probably arises from one or more foci of high-grade SIL (HSIL), as depicted in the drawing by epithelial cells crossing the basement membrane below the region of HSIL.

Anal Dysplasia as an Anal Cancer Precursor

- Comparing anal dysplasia/cancer with cervical dysplasia/cancer:
 - Same HPV risk types (16/18)
 - Similar cytology/pathology
 - Similar cytology sensitivity
 - Same chromosomal abnormalities
 - Frequently diagnosed simultaneously
 - Established progression of perianal Bowen's disease
 - **No randomized controlled trial**

SUN Study

- Observational prospective cohort study looking at annual incidence of abnormal cytology after negative cytology in 700 HIV-infected participants in 4 US cities
- Incidence of abnormal anal cytology at follow up
 - MSM – 16.2 per 100 person years
 - Women – 11.1 per 100 person years
 - MSW – 9.9 per 100 person years
- Factors associated with incident abnormal anal cytology
 - MSM
 - Age > 36 years
 - Unprotected RAI
 - Detection of HPV genotypes at baseline (LR or HR)

Risk Factors for Progression from LSIL to HSIL

- HIV infection with CD4 count <200 cells/ μ L
- Infection with multiple HPV types
- Prevalent high-level of high-risk HPV DNA
- Abnormal anal cytology (HSIL $>$ LSIL)
- Abnormal HRA examination

HSIL Regression, and HAART Effect

- Previously generally accepted that HSIL rarely regresses
 - Study from the SPANC group showed ~25% regression of HSIL (AIN 2/3)
- More recent studies indicating a protective effect of ART (or early ART) and a stable sexual relationship

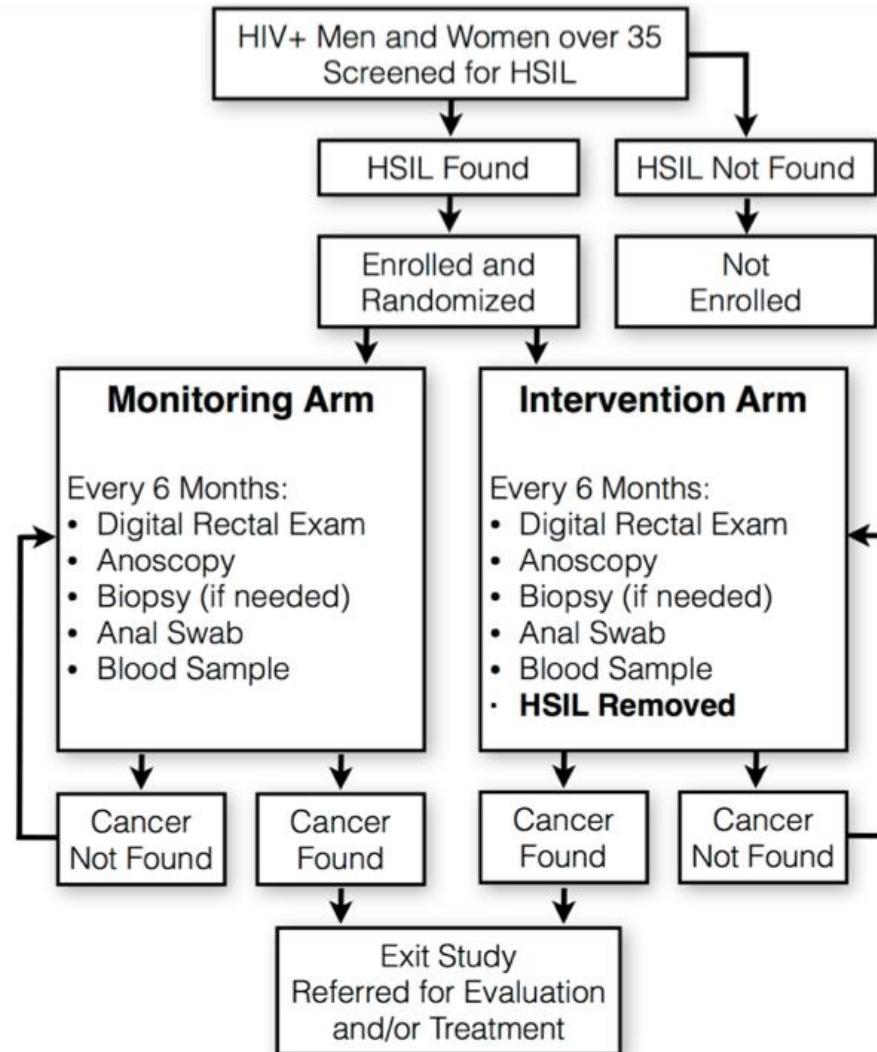
Progression of HGAIN to Cancer

- 5/32 (16%) HIV-infected patients with HGAIN at a mean of 6 years of follow up
 - Condyloma Rx only
- 5/36 (14%) HIV-infected patients with perianal HGAIN after a mean of 2.2 years of follow-up
 - Imiquimod and some surgery
- 8/55 (15%) with AIN 2/3 developed cancer with a median follow-up of 5 years
 - No Rx
- 2/184 (1%) in UCSF cohort of extensive HGAIN developed anal cancer
 - Aggressive surgery and office based Rx
- 21 patients were identified with cancer from a previously-biopsied site of HGAIN at UCSF

ANCHOR Study

- Objective: To show that treatment of anal HSIL will reduce the risk of invasive anal cancer
- Randomized clinical trial enrolling 5000 HIV-infected adults age 35 or older with anal HSIL
- One arm receives best available treatment of anal HSIL vs. active monitoring without treatment
- Endpoint: Anal cancer

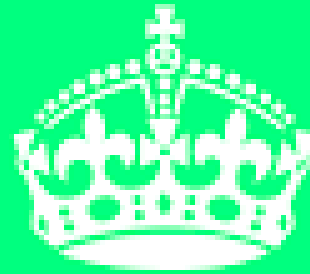
ANCHOR Study Design



Estimated < 50
develop cancer

Controversies in Anal Cancer Screening

- General acceptance that HSIL precedes anal cancer but most people with HSIL will never develop cancer
- Treatments for HSIL are not well studied but are clearly less effective than those for cervical intraepithelial neoplasia
- Assessment by HRA and treatment of HSIL can be difficult
- Few data on non-HIV infected immunosuppressed populations (solid organ transplant recipients, stem cell transplants)
- Not yet recommended by national organizations setting standards for health care maintenance



**KEEP
CALM
AND
START THE
CONVERSATION**

The Conversation

- Consider:
 - Side effects of treatment
 - Quality of life
 - Regression
 - Recurrence
 - Anal cancer (late) presentation
 - Anal cancer treatment morbidity

Surgery and Electrofulguration

- HRA directed surgical treatment
- 29 HIV-infected and 8 uninfected MSM
- Mean age 45+/- 8 yrs
- Follow up approx. 30 months
 - HIV uninfected: no recurrence
 - HIV-infected: 23/29 (79%) had recurrent or persistent HSIL
 - 6 were re-treated and 4 recurred
- No SAE

80% Trichloroacetic Acid



80% Trichloroacetic Acid

- HIV-infected MSM
- TCA applied 5 x with Q-tip
 - 98 lesions in 72 patients
 - 77 (78.6%) resolved to LSIL or normal
 - 48 (49.0%) and 27 (27.6%) lesions resolved with 1 and 2 TCA treatments
 - 8 (15.1%) of 53 patients had a lesion that recurred at the index site
 - No SAEs

Infrared Coagulation



Infrared Coagulation

- HIV-infected men and women
- 66 patients with HSIL treated (cytology ASCUS (14%), LSIL (27.5%), HSIL (8%))
- At 12 months
 - all patients had normal anal cytology
- At a mean of 30 months (18-43)
 - 7/66 (13%) had HSIL

Electrocautery

- 83 HIV-infected MSM
- Assessed at 6-8 weeks following procedure/s
 - Complete response: 27 (32%)
 - LSIL: 28 (34%)
 - Persistence 28 (34%)
- At a mean of 30 months, 14/55 (25%) had HSIL
- No SAE

5% Imiquimod



5% Imiquimod

- Double blind randomized placebo controlled study in HIV-infected participants
 - 64 enrolled and 53 completed (1 d/c due to S/E)
 - Self applied imiquimod (28)/placebo (25) 3 x per week x 4 months
 - Anal cytology, HRA and biopsy at 6 months
 - Imiquimod: 4 resolved, 8 LSIL (43%)
 - Placebo: 1 resolved (4%)
 - Open label: 5 cleared and 4 LSIL
 - Overall 63% response during follow up to 36 months

5-Fluorouracil



5% Fluorouracil

- 11 HIV-infected patients with internal anal dysplasia
 - 6 (55%) clinical improvement with reduction of volume
 - 3 (27%) improvement of dysplasia grade
 - 8 (73%) had mild/moderate perianal irritation requiring dose reduction in 6

Cidofovir



1% Cidofovir

- 24 HIV-infected men and 9 HIV-infected women with anal and vulvar HSIL ≥ 3 cm²
- Topical application for 6 2-week cycles
- 26 (79%) completed treatment
 - 5 (15%) complete response
 - 12 (36%) partial (over 50% reduction in size)
 - 7 (21%) stable
 - 2 (6%) progressed
- Burning/irritation in 25, ulceration in 13

Radiofrequency Ablation

- 21 HIV-uninfected participants
- HSIL less than 50% circumference
- HRA every 3 months for 12 months
 - 6 (29%) recurrence
 - 4 (19%) had persistence of index lesion at 3 months
- New procedure and impact of learning curve on lesion Rx efficacy
- No SAE

Treatment of HSIL in HIV-infected MSM

Treatment	Efficacy
Excision/Electrofulguration	20%
Infrared coagulation	65-70%
Electrocautery	66%
Radiofrequency ablation	76%
Trichloroacetic acid	70%
Imiquimod	60-70%
Cidofovir	51%
Combination	70%

Chang 2002, Cranston 2008, Goldstone 2005, Singh 2009, Fox 2010, Kreuter 2008, Nathan 2008, Goldstone 2016, Burgos 2015, Stier 2013

Recurrence by Study

Treatment	Recurrence
Excision/Electrofulguration	79%
Infrared coagulation	50%
Electrocautery	25%
Radiofrequency ablation	29%
Trichloroacetic acid	15%
Combination Rx in HIV-infected patients	1 year: 50% and 2 year: 70 %

Summary of Treatments

- Ablative treatments are commonly used
 - Generally well tolerated
 - Disease recurrence is very common
 - Responses are suboptimal
- Topical treatments are alternatives
 - 5 fluorouracil, imiquimod, and application of TCA are used in practice.
- Prospective studies are lacking, better treatments are needed



**KEEP
CALM
AND
DO NO
HARM**

Summary

- Partner with patients to understand their treatment needs
- Discuss the range of treatment modalities
- Prioritize minimally invasive treatment
- Plan for recurrence and re-treatment
- Educate on symptoms suggestive of progression

Future

- Prophylactic vaccination
- Therapeutic vaccination
- Increase anal cancer awareness in at-risk populations
- Rationalize treatment based on biomarkers
- Normalize DARE as a routine aspect of physical examination in at-risk populations

Thank You