Prevention of HPV-related Cancers: An Update

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New York City, New York

2022 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

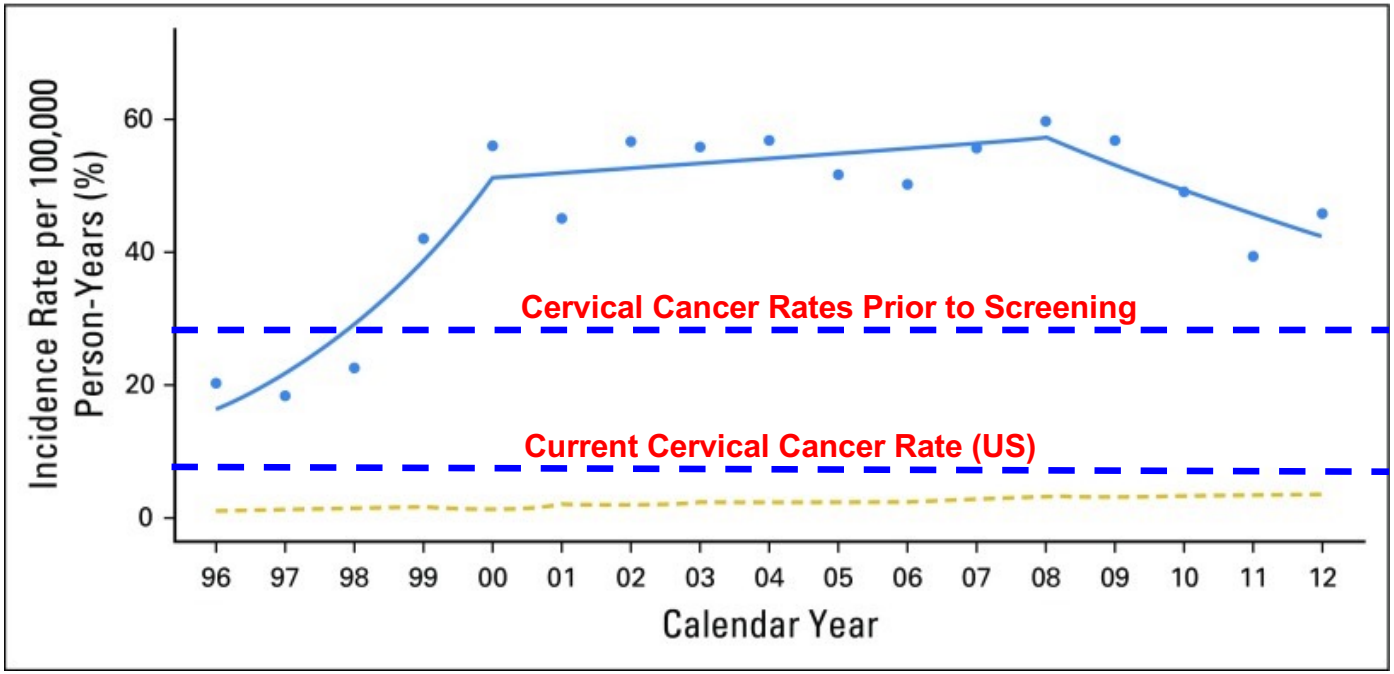
Dr Wilkin has served as an ad hoc consultant for Merck. Dr Wilkin receives grant support paid to his institution from Merck. (Updated 10/13/22)

Learning Objectives

After attending this presentation, learners will be able to:

- Describe populations to be considered for anal cancer screening
- Discuss ANCHOR results and the evidence to support anal cancer screening
- List characteristics associated with increased progression to cancer

Anal Cancer Rates in People with HIV



Blue (line and dots) = Observed anal cancer rates in PWH
Yellow line = Observed anal cancer rates in the general population

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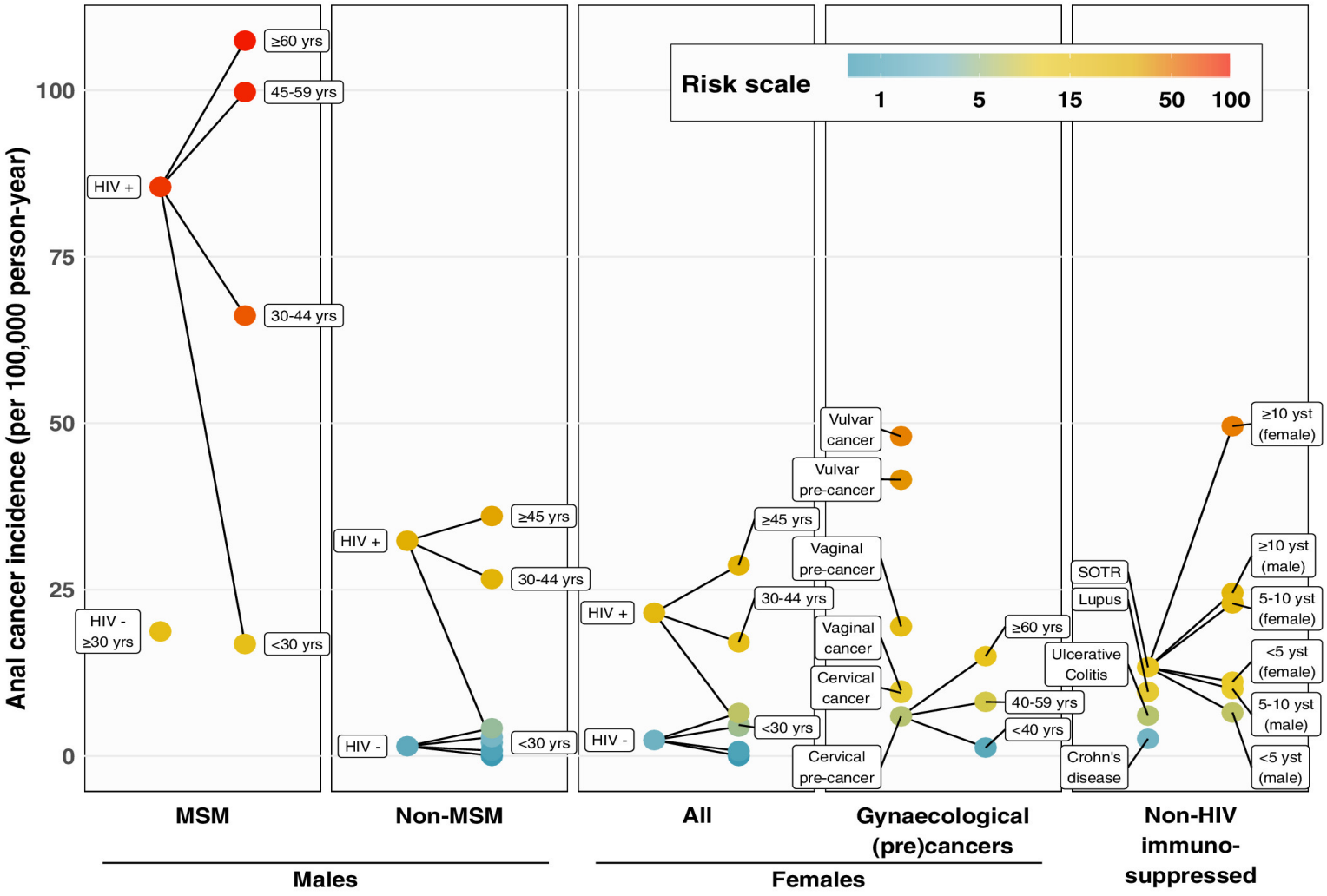
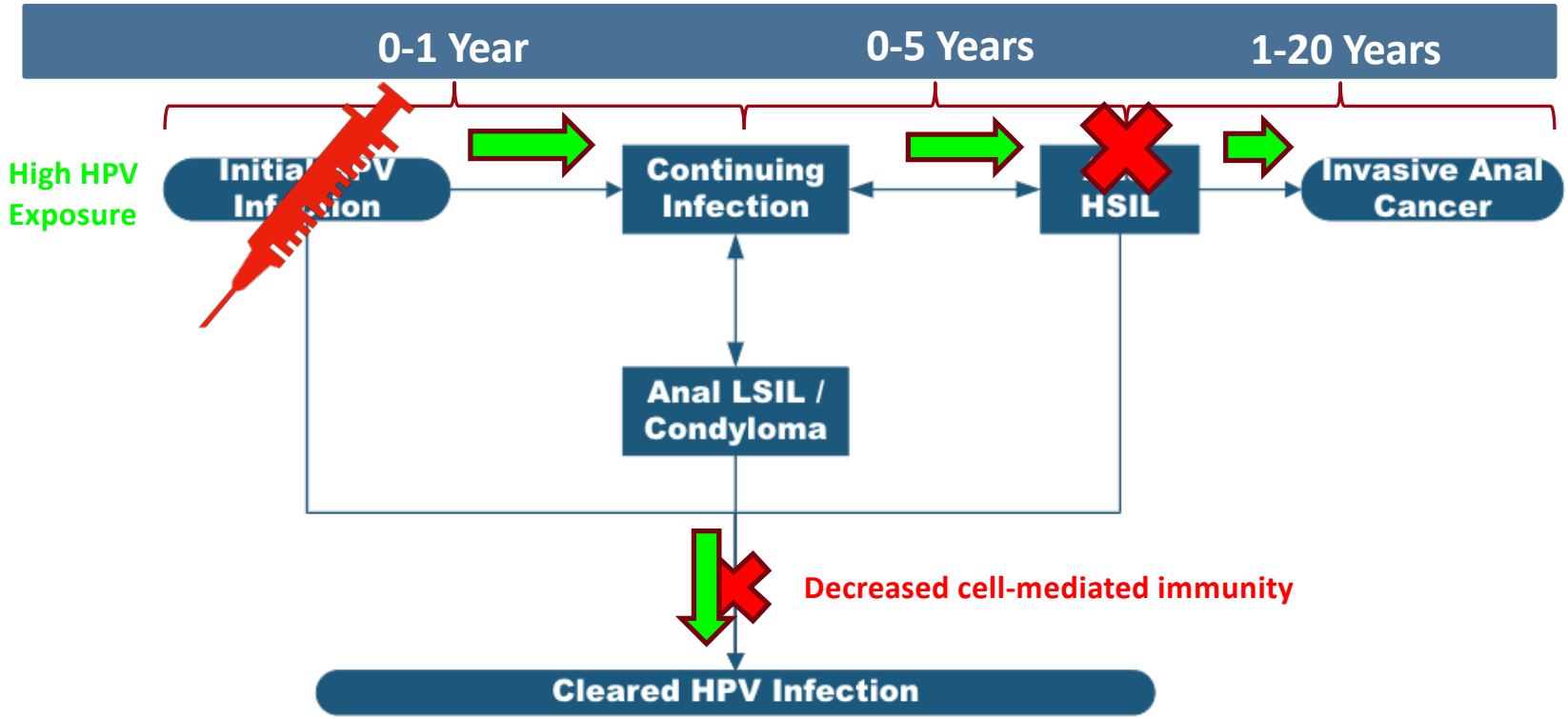
Colon-Lopez, Shiels et al. J Clin Oncol. 2017



Clifford GM, et al. Int. J. Cancer. 2021; 148: 38-47.

Natural History of HPV Infection and Progression to Anal Cancer



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Adapted from Pinto AP, Crum CP. Clin Obstet Gynecol. 2000;43:352–362

Case: Anal cancer screening

- **This a 52 year-old male living with HIV recently referred for primary care. He is virally suppressed with a CD4 of 425 cells/mm3. He reports being diagnosed in 1999. He was not engaged in care until 2010. His nadir CD4 was 45 cells/mm3 and he was hospitalized for PJP pneumonia. He is a former smoker.**

- **He has heard about anal cancer screening. He has a history of anal warts years ago. He reports some anal bleeding and palpable nodule.**

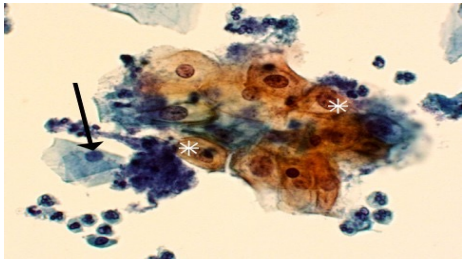
slido

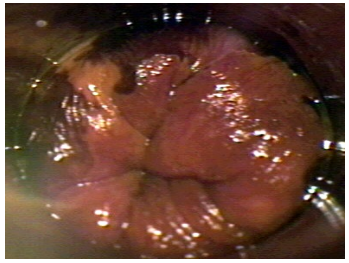
Which of the following tests would not be an appropriate component of anal cancer screening for this person?

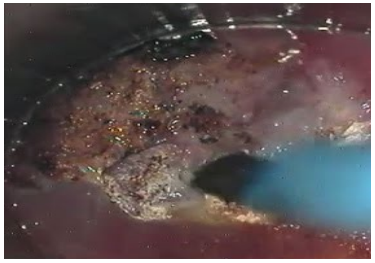
ⓘ Start presenting to display the poll results on this slide.

Anal Cancer Prevention: Screening

- **Goals: Identify and remove pre-cancerous areas of the anus (and perianus) to prevent invasive cancer**
  - **SCREEN with anal cytology (+/- HPV testing) AND digital anorectal exam (DARE)**
  - **DIAGNOSE anal HSIL with High Resolution Anoscopy (HRA)**
  - **TREAT anal HSIL with ablation or topical therapy**
- **Anal cancer is treated with chemotherapy and radiation**







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Anal Cytology as a screen for anal cancer

- **Performance (≥ ASCUS)**
  - **Sensitivity 69 to 93% and Specificity 23 to 59%**
- **Recommendations:**
  - **No preps, no anal sex 48 hours prior**
  - **Prior to DARE or HRA (no lubricant)**
  - **Moistened polyester swab**
  - **Separate anal verge**
  - **Insert to rectal wall**
  - **Spiral motion with pressure and withdraw slowly (10 s)**
  - **Adequate agitation in cytology medium**

- **In general, refer all abnormal cytology in PWH for HRA: ASC-US, LSIL, ASC-H, HSIL**

- **https://youtu.be/YyzmLYFc7Yc**

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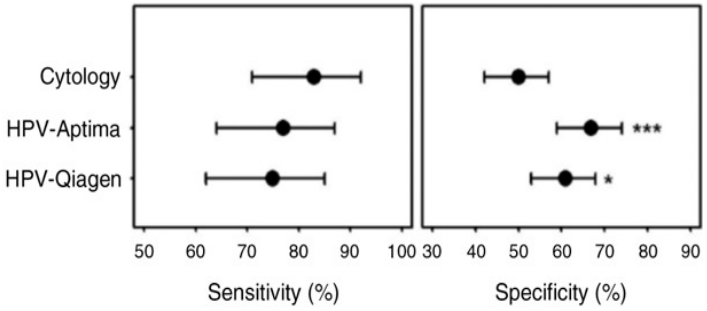
Chiao EY, Lensing SY. AIDS. 2020 Dec 1;34(15):2249-2258
Chiao EY, Giordona TP. Clin Infect Dis 2006;43(2):223-33

HPV-Based Screening

- **High prevalence anal HPV infection in men who have anal intercourse**
  - **Perhaps useful in those with ASCUS cytology**
- **High-risk HPV screening in women with HIV: 41% to 45% prevalence:**



Xpert HPV Optimization	Sensitivity, % (95% CI)	Specificity, % (95 % CI)
Anal Cytology	87 (74, 94)	49 (40, 57)
Unmodified Xpert	89 (78, 96)	49 (40, 57)
Xpert Optimized by Channel and ROC	75 (61, 85)	84 (76, 89)
Xpert Optimized using Ct and Recursive Partitioning	75 (61, 85)	86 (80, 92)

- **Thought to have good negative predictive value (NPV) but more research needed**
- **Reimbursement inconsistent**
- **Not FDA approved**

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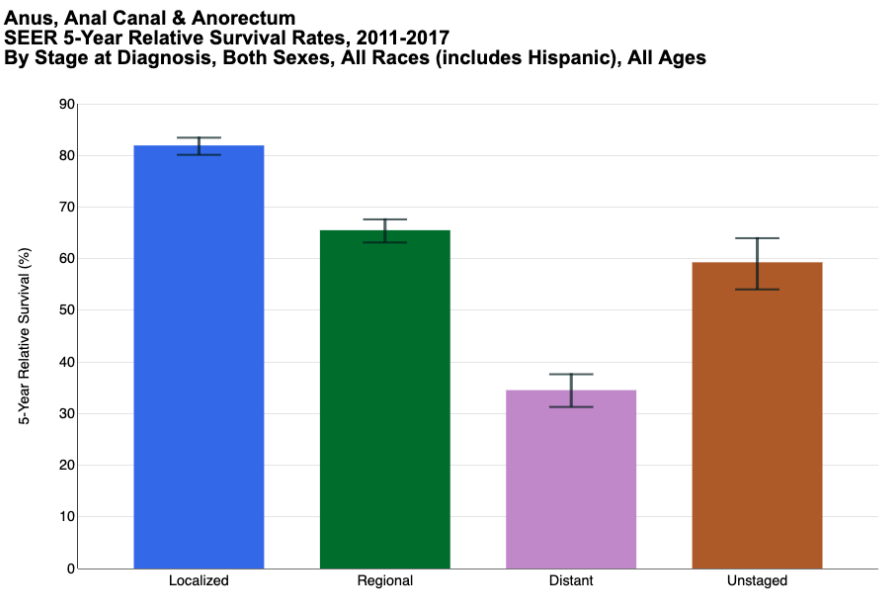
Burgos J, Hernández-Losa. AIDS 2017;31(16):2227-2233
Chiao EY, Lensing SY. AIDS. 2020;Dec 1;34(15):2249-2258
Ellsworth G, et. al. J Acquir Immune Defic Syndr. 2021;87(3):978-984.

Digital Anorectal Exam (DARE)

- **Anal cancer survival related to stage**
  - **Superficially invasive cancer is treated only surgically**
- **Examine:**
  - **Circumference and length of anal canal and distal rectum**
  - **Anal margin: 5 cm distal to anal verge**
  - **Prostate or Pouch of Douglas**



Guidelines

Hillman RJ, Berry-Lawhorn JM, J Low Genit Tract Dis. 2019 Apr;23(2):138-146

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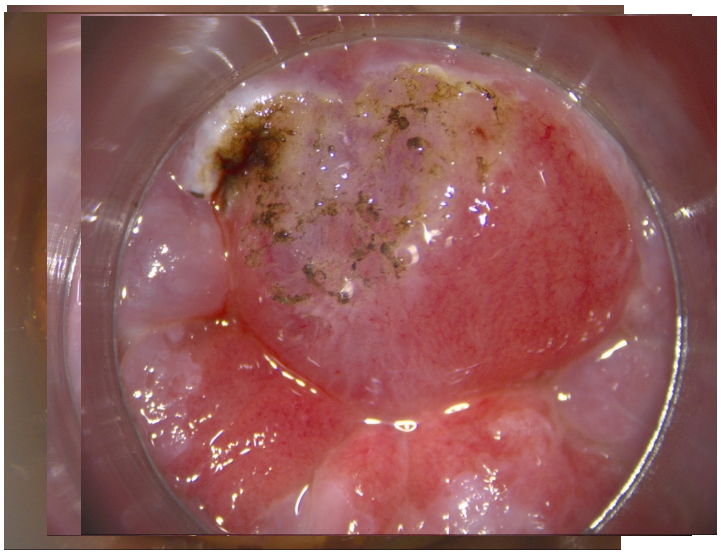
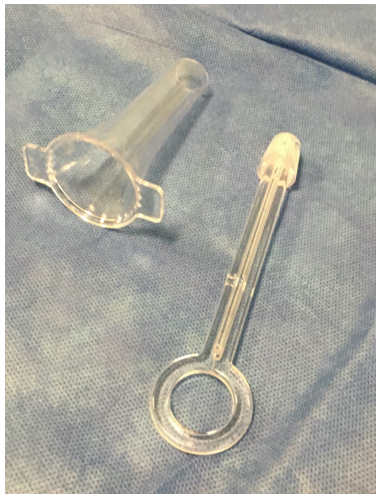
High Resolution Anoscopy - HRA





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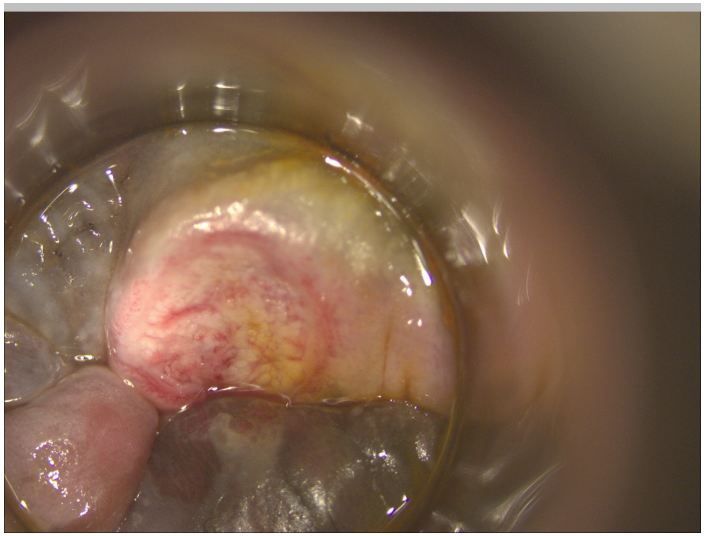
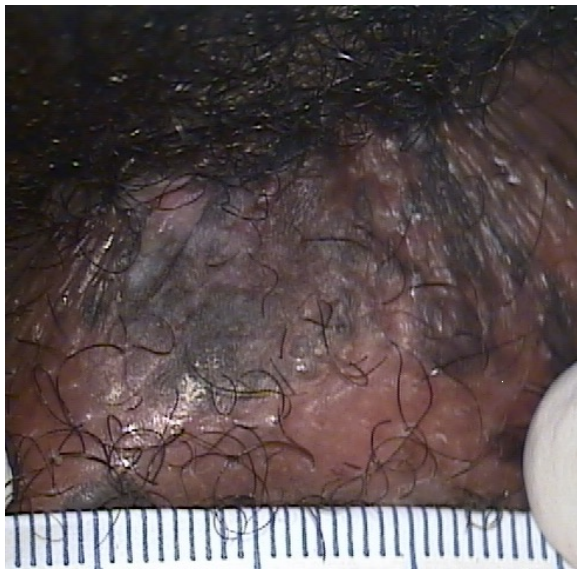
High Resolution Anoscopy - HRA



Invasive cancer



Perianal HSIL

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Why Study Anal Cancer Prevention?

- **Treatment of cervical HSIL reduces the incidence of cervical cancer**

- **Why would a similar strategy not work in the anus?**
  - **Lesions are large, multifocal**
  - **Lesion recur, new lesions appear**
  - **HSIL eradication is difficult**
  - **Issues with tolerance/safety of high resolution anoscopy (HRA) and HSIL ablation/treatment**

AMC-076: Randomized Clinical Trial of Infrared Coagulation of Anal HSIL

	IRC	Control	P-value*
Overall CR Rate of Index HSIL	62% (37/60) 95% CI, 48-74%	30% (18/60) 95% CI, 19-43%	<0.001
Overall CR/PR Rate of Index HSIL	82% (49/60) 95% CI, 70-90%	47% (28/60) 95% CI, 33-60%	<0.001
Free of HSIL at 12-months	71% (36/51) 95% CI, 56-83%	28% (16/57) 95% CI, 17-42%	<0.001

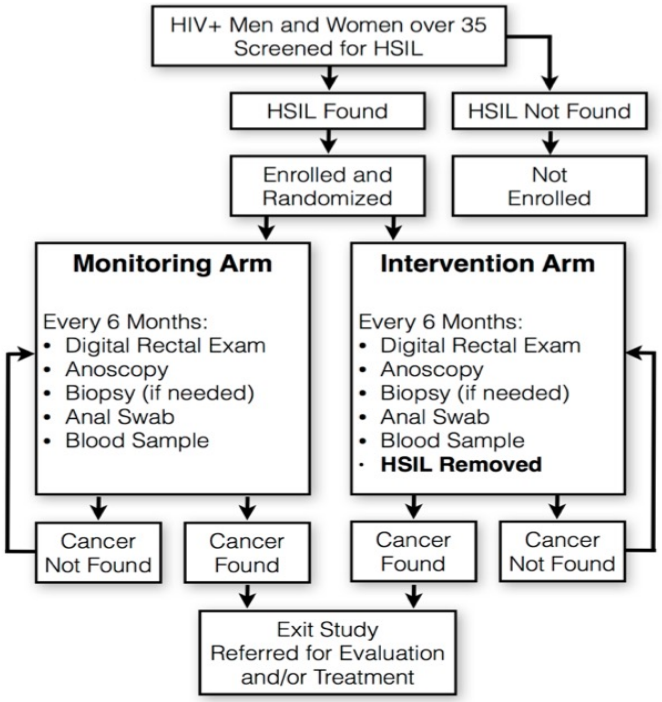
* One-sided (α = .025) stratified Mantel-Haenszel chi-square test.
Strata were Laser Surgery Center (n=71) and remaining 5 sites (n=49)

Goldstone SE, Lensing SY, et. al. Clin Infect Dis. 2019. 68(7) 1204-1212.

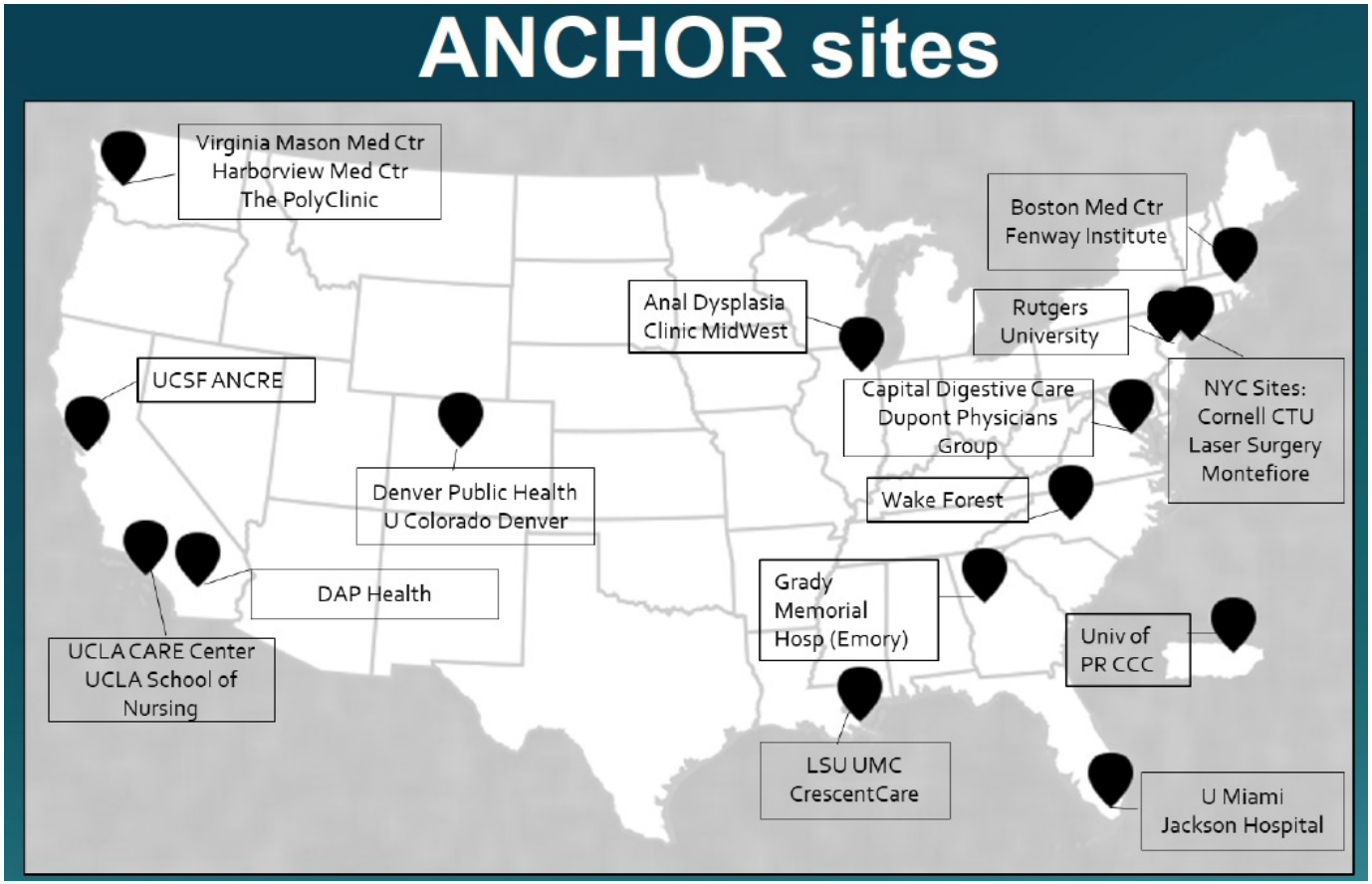
the ANCHOR study

Primary Endpoint: Time to anal cancer

Secondary Endpoint: Adverse events related to treatment of HSIL



https://clinicaltrials.gov/ct2/show/NCT02135419
https://anchorstudy.org/



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Methodology

- **Visits every 6 months**
  - **Every 3 months if concern for cancer**

- **Collect**
  - **Anal cytology**
  - **Swabs**
  - **Blood (serum)**
- **Digital anorectal exam**
- **HRA**

Methodology

Treatment Arm

- HSIL treated:
  - **at Visit 1**
  - **at interim visits if found on biopsy at 6-month visits**
- Modalities (14% treated with > 1 modality):
  - **Electrocautery (93%)**
  - **Infrared coagulation (6%)**
  - **Treatment with anesthesia (5%)**
  - **Topical 5-fluorouracil (7%)**
  - **Topical imiquimod (1%)**

Active Monitoring Arm

- HSIL biopsied annually
  - **Or more frequently with concern for progression to cancer**

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)

Palefsky, et. al. N Engl J Med. 2022;368(24):2273-2282

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/mm^3‖	602 (393–827)	607 (410–837)
Nadir CD4 count — no. (%)**		
≤200 cells/mm^3	1130 (50.7)	1121 (50.5)
>200 cells/mm^3	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)

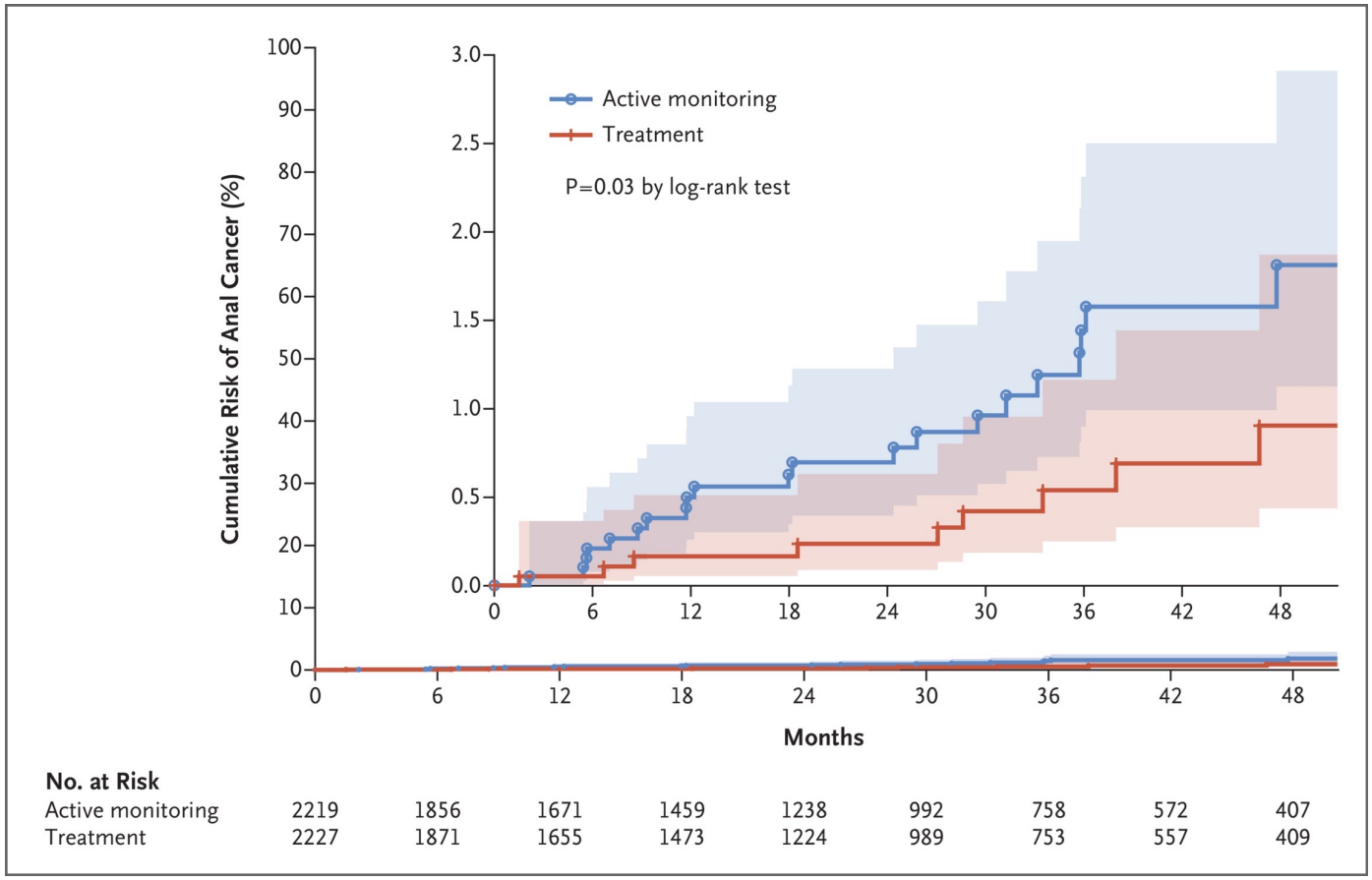
Palefsky, et. al. N Engl J Med. 2022;368(24):2273-2282

Results

the ANCHOR study

	Treatment	Active Monitoring	Overall
Invasive Cancer Cases	9	21	30
Cancer Incidence (per 100,000 PY)	173	402	-
Months of follow-up (median, IQR)	25 (12-42)	27 (12-42)	25.8

Treatment resulted in a 57% reduction in anal cancer (95% CI, 6% to 80%, P=.029)



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Palefsky, et. al. N Engl J Med. 2022;368(24):2273-2282 Slide 25

Case continued

- **His anal cytology showed atypical squamous cells suggestive of HSIL**
- **His HRA found HSIL that extended about 75% of the circumference on the SCJ; 2 areas of condyloma were noted as well**
- **He had 2 large perianal HSIL areas as well**

slido

Which of the following appears to be the strongest predictor of developing anal cancer based on ANCHOR data?

ⓘ Start presenting to display the poll results on this slide.

Risk Factors Associated with Cancer Development

- **Lesion Size (Overall)**
  - **HSIL involving ≤ 50% vs > 50% of anus/perianus: 185 vs 1047 / 100,000 PY.**
  - **HR 5.26 (95% CI, 2.54 to 10.87)**
- **Monitoring Arm**
  - **Smoking (OR 3.32, p=0.009)**
  - **Lesion Size (OR 8.14, p<0.001): > 50% vs ≤ 50%**
  - **Years from HIV diagnosis**

ANCHOR: Other Findings

HSIL Regression (Monitoring Arm) at 1 year

- **~33 to 34%**

HSIL Persistence (Treatment Arm) at 1 year

- **38% (males) and 26% (females)**

 # Needed to Screen to Prevent One Case

Anal Cancer	Cervical Cancer
• 892 PWH • 2-3 year period	• 2,436 women • Lifetime

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Palefesky. IANS Conference. NYC 2022
Kim JJ et el. JAMA 2018; 320: 706-14

Conclusions

- **Rate of progression of anal HSIL to cancer in PWH is HIGH**
- **Treatment of anal HSIL is an effective strategy to reduce the incidence of anal cancer in persons with HIV**
- **Recommendations to screen for and treat anal HSIL should be included in guidelines as standards of care for PWH**

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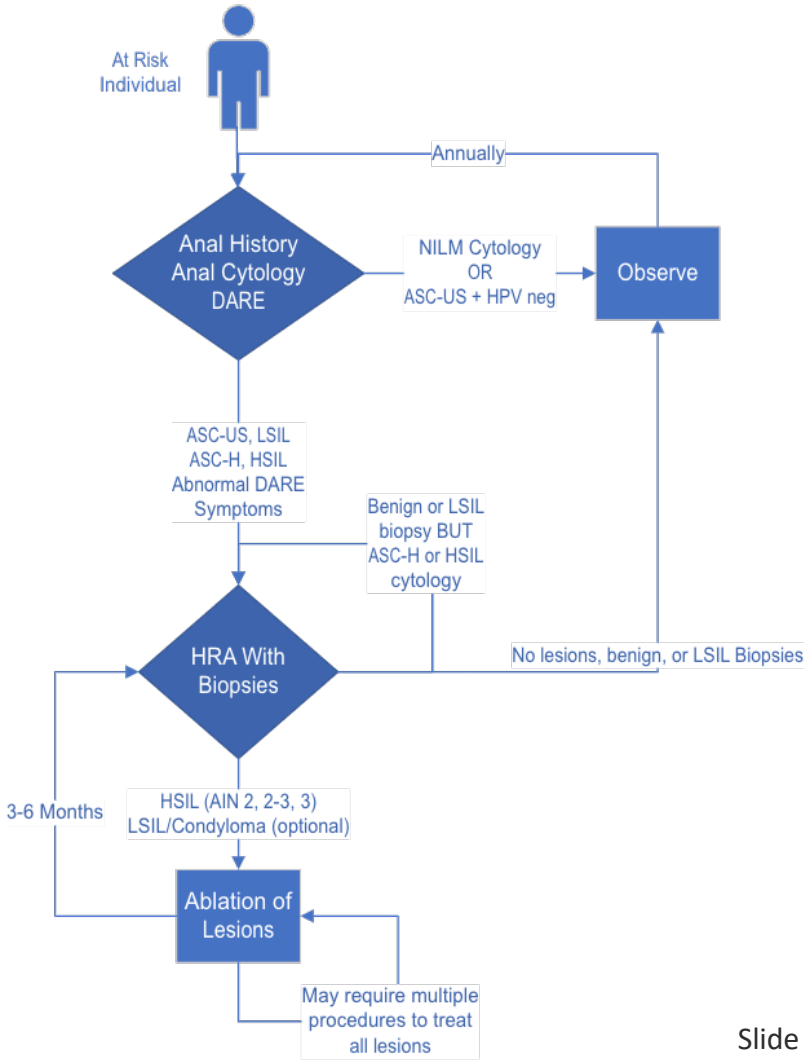
Suggested Screening Algorithm

- **Annually with anal cytology +/- high-risk HPV testing**
- **After ablation of anal HSIL: repeat HRA at least every 6 months for the first year**
- **Surgical referral may be required for advanced or complicated disease**
- **Topical therapy may have a role but is not included in this algorithm**



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Persisting Controversies

- **There is a need to improve anal HSIL treatment efficacy**
  - **Improve clinical skills**
  - **Novel or adjunctive therapies**
- **There is not widespread access to quality HRA**
  - **Need for large scale training programs**
  - **Improved screening tools (biomarkers) and algorithms**
  - **No proven biomarkers for HSIL regression/progression**
- **Can ANCHOR results be extrapolated to other at-risk groups?**
- **Need for updated cost-effective analyses**

What to Do?

- **Access to HRA?**
  - **Screen patients (symptoms, cytology, DARE, +/- HPV) and refer for HRA**
- **No access to HRA?**
  - **Symptom-based screening and DARE**
  - **Develop or expand local HRA programs**

2012-2022
Celebrating a decade of service and education
International Anal Neoplasia Society

https://iansoc.org/HRA-Course-Overview

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Study participants

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the ANCHOR study

AMC AIDS Malignancy Consortium

Q and A Session

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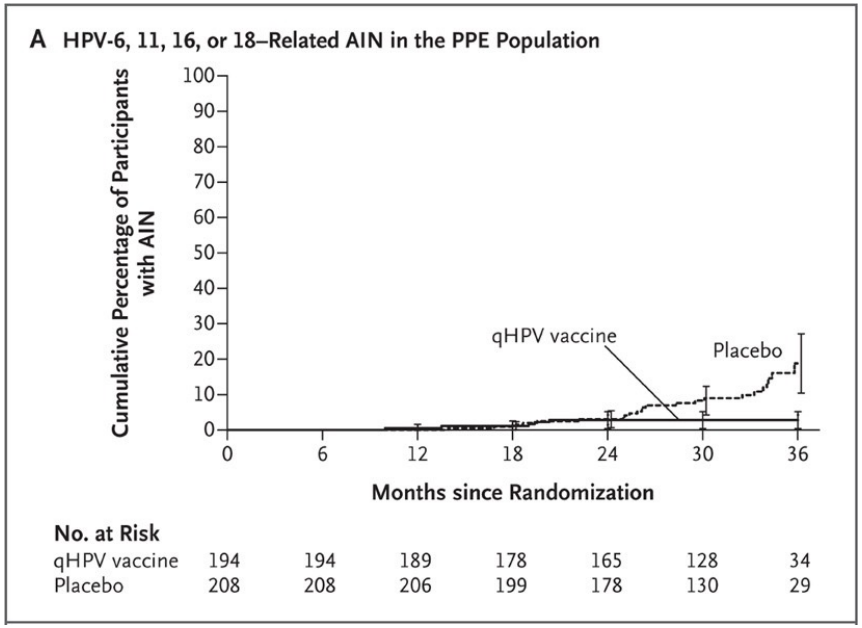
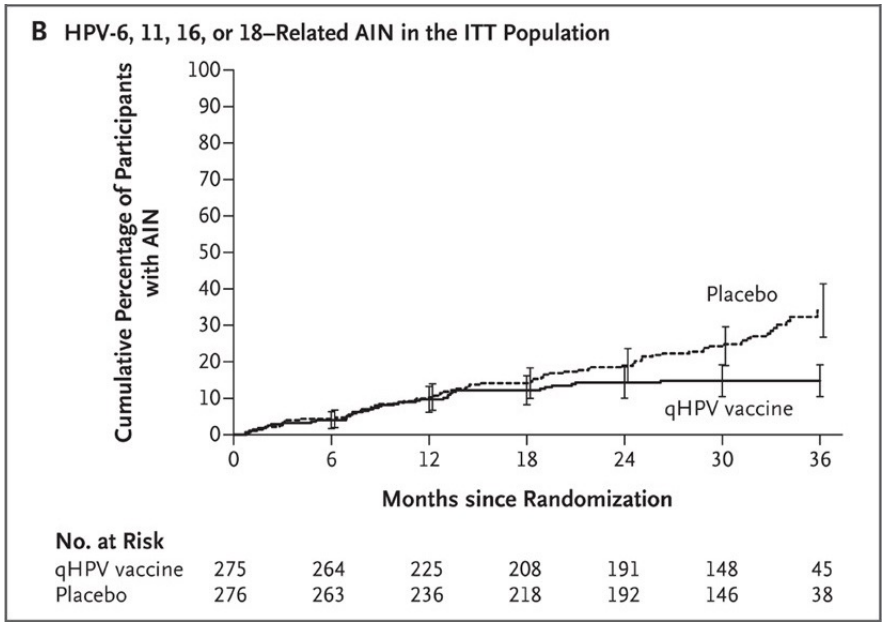
HPV Vaccination

An Update

Prevention of Anal Cancer with HPV Vaccination



Excludes those with vaccine type infections at baseline



Includes those with vaccine type infections at baseline

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Palefsky JM et al. N Engl J Med 2011;365:1576-1585

ACTG 5298: Randomized Placebo-Controlled Trial of Quadrivalent HPV Vaccine (qHPV)

Outcome	4vHPV (n)	Placebo (n)	HR (95% CI)
Persistent anal HPV, or single detection at last visit	26	33	0.75 (0.45, 1.26)
Persistent anal HPV	13	17	0.73 (0.36, 1.52)
Anal HSIL	46	45	1.0 (0.69-1.44)
Persistent oral HPV	1	8	0.12 (0.02, 0.98)

*Persistent infection: qHPV-type (6, 11, 16, 18) present at 2 consecutive visit NOT present at baseline

Wilkin TJ, Chen H, et. al. Clin Infect Dis. 2018. 67(9):1339-1346

Basis for US FDA Indications of 9vHPV for Adults up to Age 45

- **V501-019: 3819 Colombian women ages 24 to 45 with *no history* of cervical disease or genital warts in the last 5 years.**
- **Efficacy to prevent combined endpoint of prevention of genital warts, CIN, or persistent infection due to qHPV types (6, 11, 16, 18)**

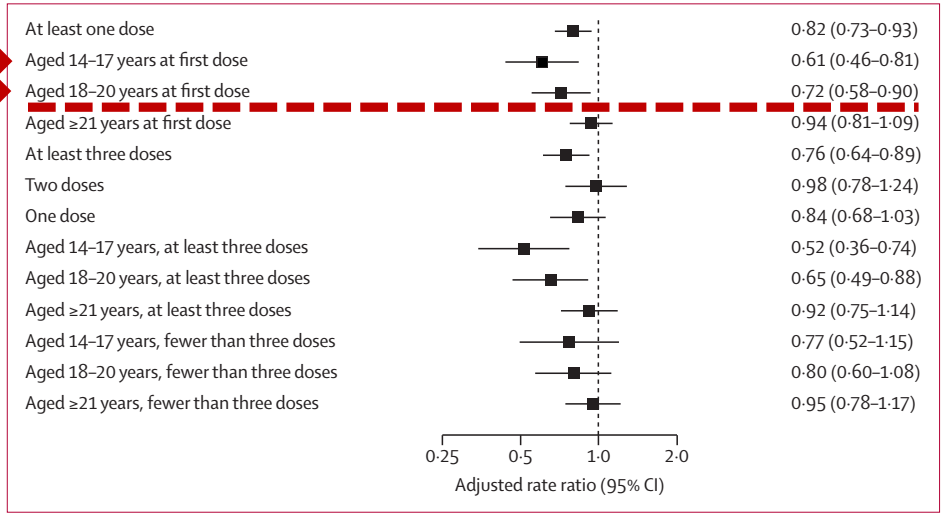
Baseline Status	Efficacy, %	95% CI
Seronegative/DNA negative (Per-protocol efficacy)	88.7	78.1, 91.3
Seropositive/DNA negative	66.9	4.3, 90.6

- **Approval of the 9vHPV vaccine based on combination of efficacy/safety/non-inferior immunogenicity in other populations**

Castellsagué X, et. al. Br J Cancer. 2011;105(1):28-37.
Montague L, et. al. Summary Basis for Regulatory Action. 2018. https://www.fda.gov/media/117054/download.

“Real World” Data of Vaccination of Adults

- **Nested case-control study: 4357 cases of CIN 2+ with 21,733 matched controls.**



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Silverberg, Leyden et al. The Lancet Child & Adolescent Health. 2018; 2(10):707-714.

Current ACIP Recommendations

Ages
9-10
11-12
13-15
16-26
27 and older

Mass HPV Vaccination of Adults (ages 30-45):

> $300,000 per QALY gained

Shared Decision Making"

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Meites E, et. al. MMWR. 2019;68(32);698-702

Prevention of Persistent Oropharyngeal HPV Infection

	4vHPV (n)	Placebo (n)	HR (95% CI)
ACTG 5298 Persistent Oral Infection[1]	1	8	0.12 (0.02, 0.98)

	2vHPV (n)	HAV (n)	VE % (95% CI)
Costa Rica Vaccine Trial: Oral Prevalence of HPV 16/18 at 4 years (study exit) n = 6,352[2]	1	15	93.3 (63, 100)

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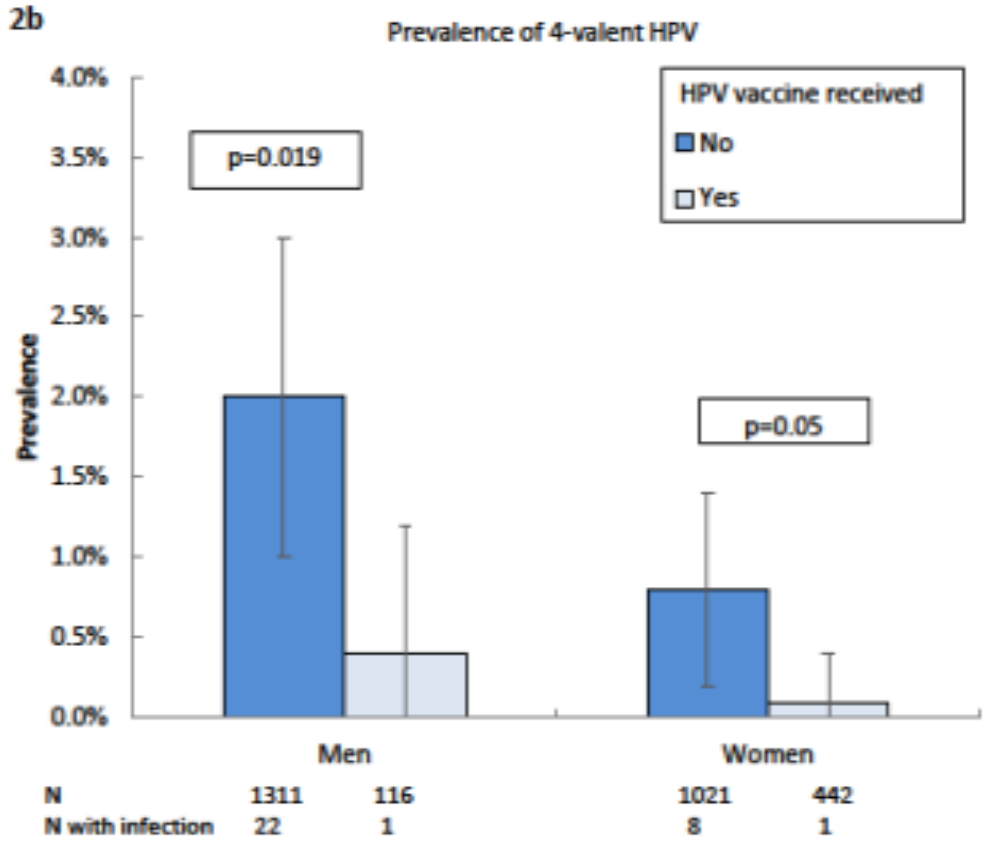
[1]Wilkin TJ, Chen H, et. al. Clin Infect Dis. 2018;67(9):1339-1346
[2]Herrero R, et. al. PLoS One. 2013;8(7):e68329



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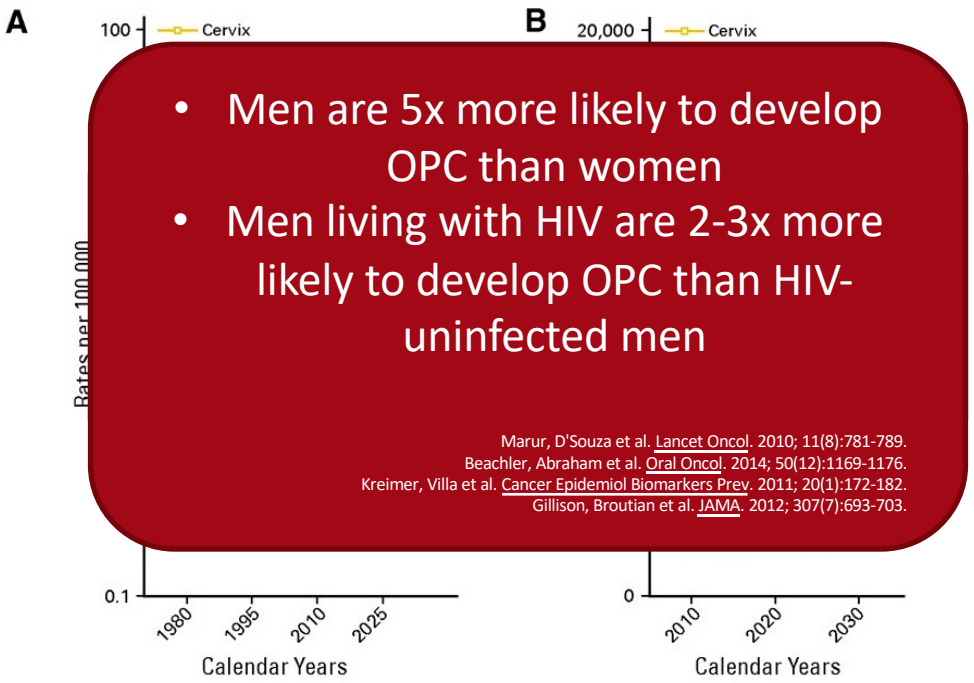
NHANES 2011-2014: Prevelance of oral qHPV types by Vaccine Status

Deshmukh KS, et. al. Ann Intern Med. 2017;167(10):714-724.

Observed and Projected Incidence Rates for Oropharyngeal Cancers (OPC) and Cervical Cancer



- Men are 5x more likely to develop OPC than women
- Men living with HIV are 2-3x more likely to develop OPC than HIV-uninfected men

Marur, D'Souza et al. Lancet Oncol. 2010; 11(8):781-789.
Beachler, Abraham et al. Oral Oncol. 2014; 50(12):1169-1176.
Kreimer, Villa et al. Cancer Epidemiol Biomarkers Prev. 2011; 20(1):172-182.
Gillison, Broutian et al. JAMA. 2012; 307(7):693-703.

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Chaturvedi AK, et. al. J Clin Oncol. 2011;29(32):4294-301.

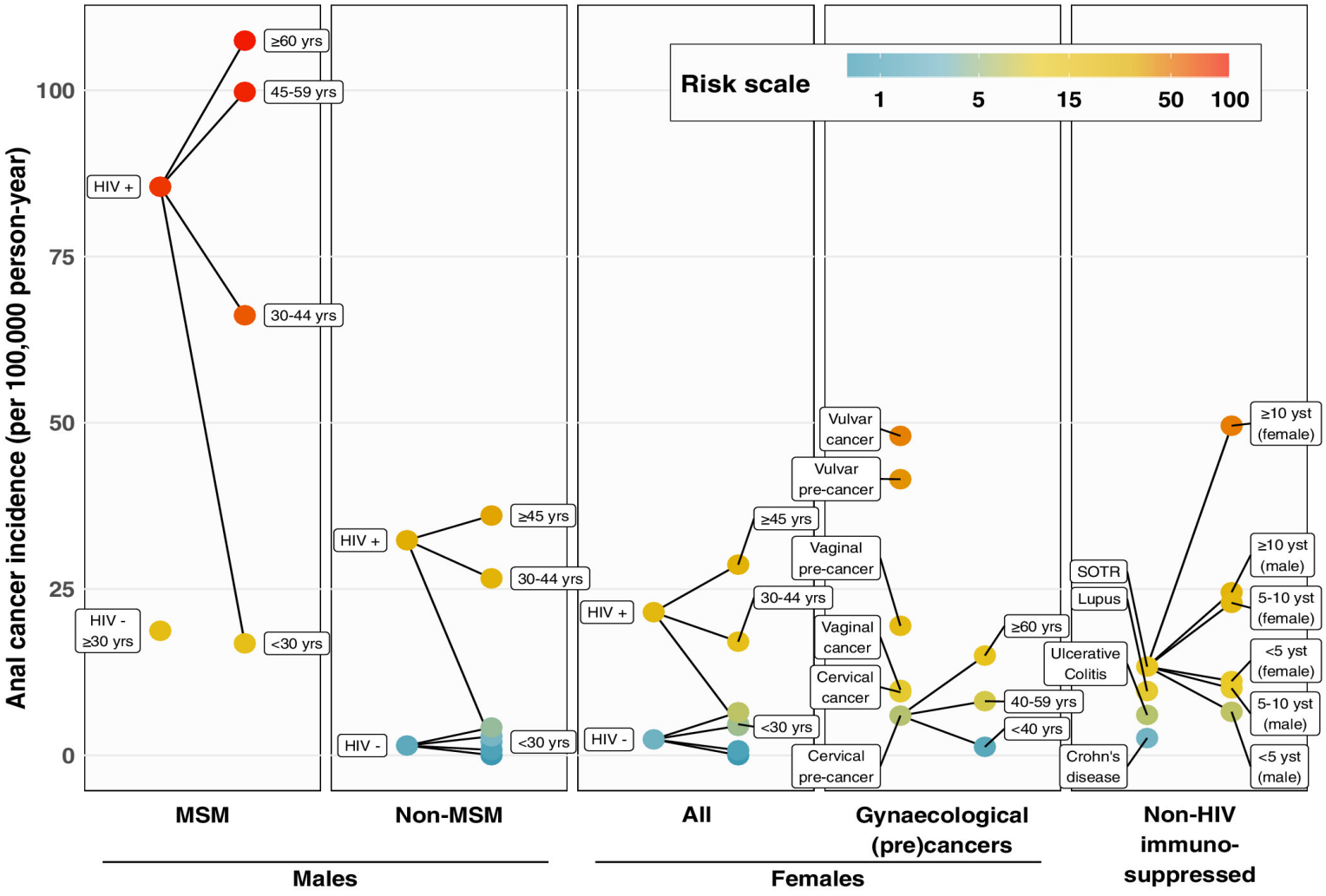
Studies of 9vHPV to Prevent Oropharyngeal Infection

9vHPV is FDA-approved for the prevention of oropharyngeal and other head and neck cancer dependent on post-marketing research:

- V503-49: Men without HIV 20 to 45 years-old (NCT 04199689)

Study of efficacy of 9vHPV to prevent oral HPV infection in Men with HIV

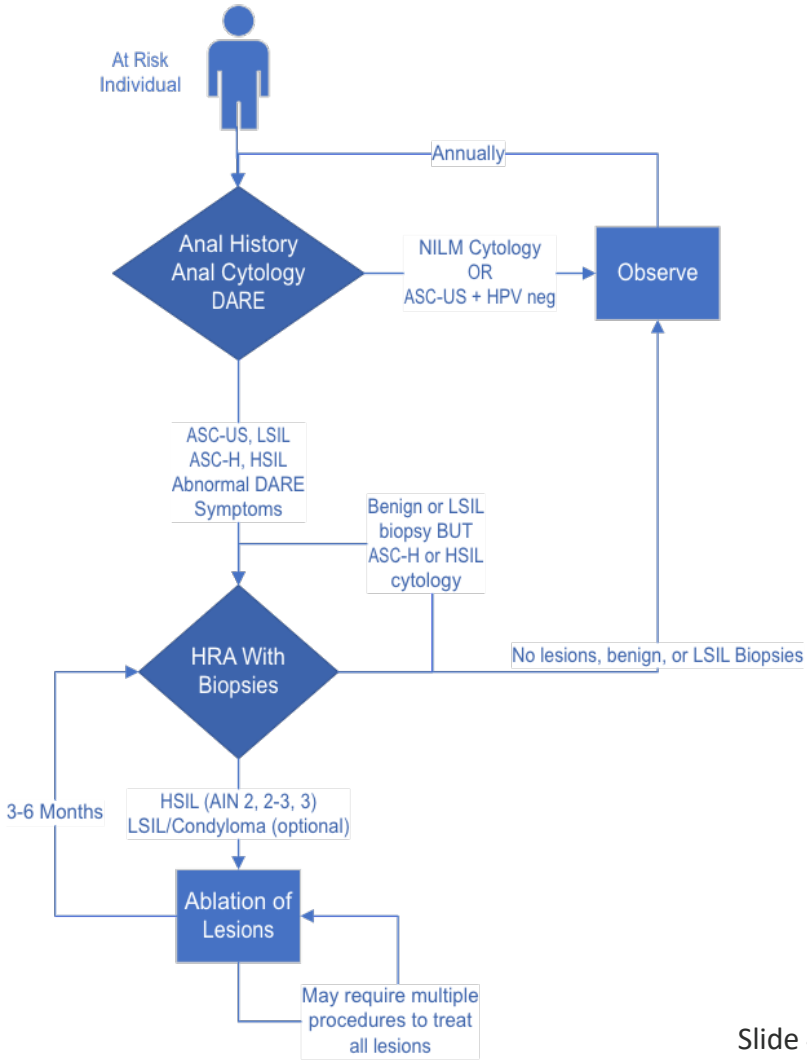
- Men living with HIV 20 to 50 years-old in Brazil, Mexico, and Puerto Rico (NCT 04255849)
- NIH/NCI: US-Latin American-Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network (ULACNet)



Clifford GM, et al. Int. J. Cancer. 2021; 148: 38-47.

Suggested Screening Algorithm

- **Annually with anal cytology +/- high-risk HPV testing**
- **After ablation of anal HSIL: repeat HRA at least every 6 months for the first year**
- **Surgical referral may be required for advanced or complicated disease**
- **Topical therapy may have a role but is not included in this algorithm**



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Q and A Session

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