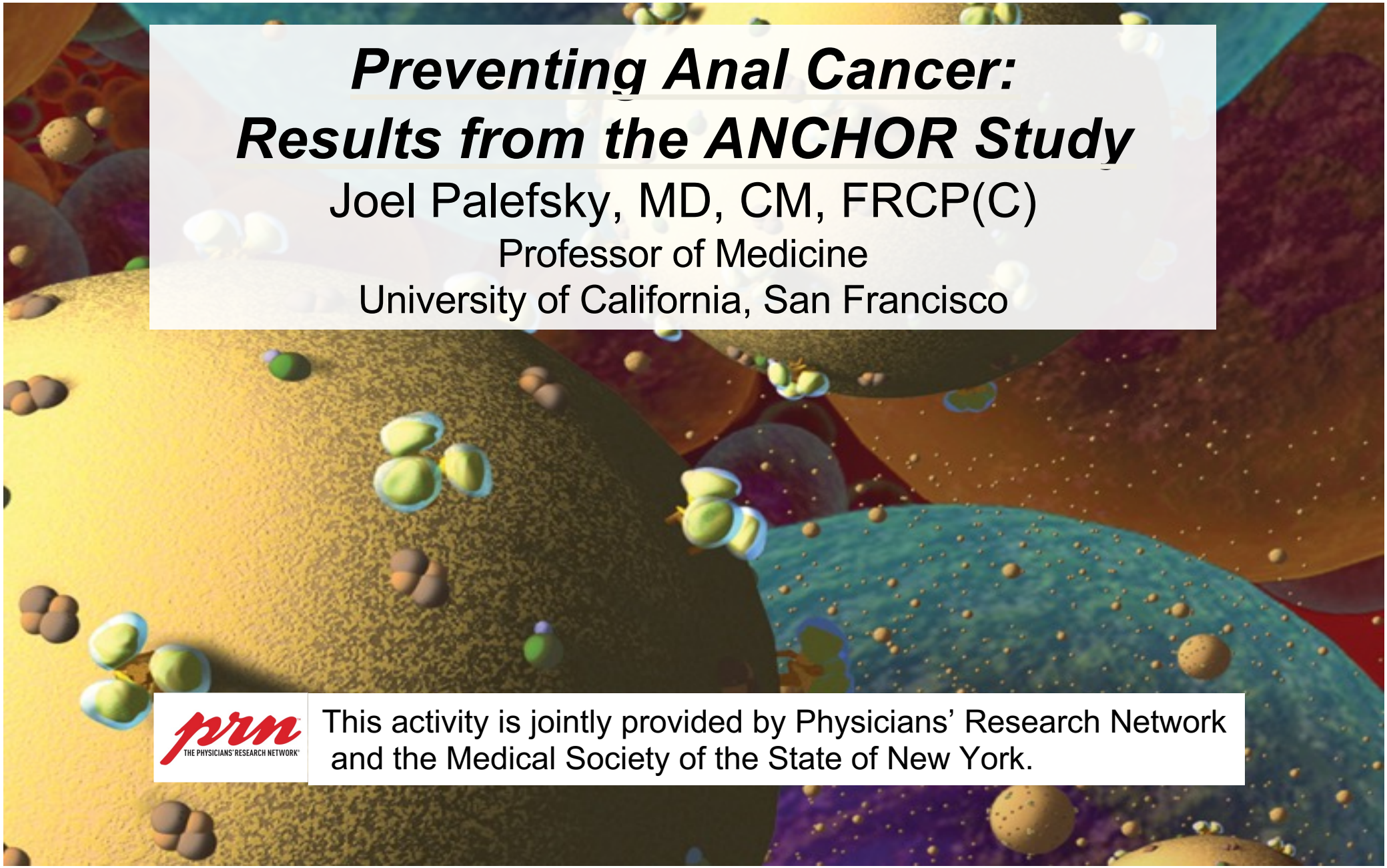

Preventing Anal Cancer: Results from the ANCHOR Study

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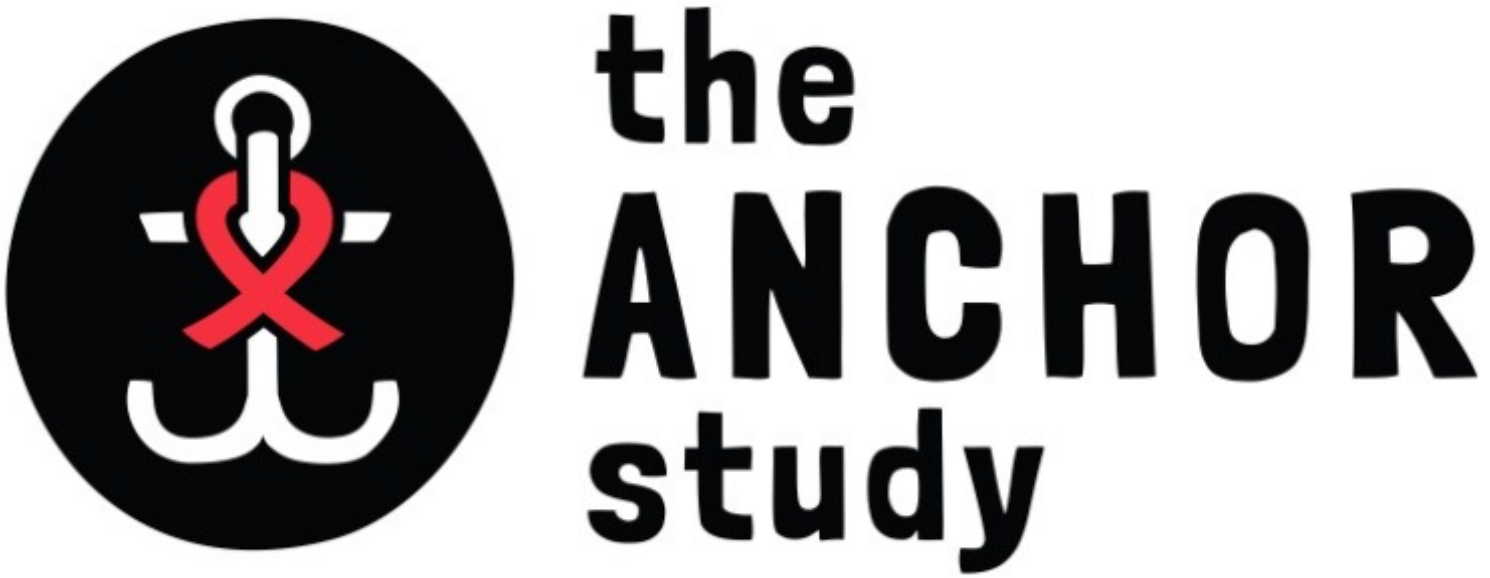
Professor of Medicine
University of California, San Francisco

This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.



The ANCHOR Investigators Group
Protocol A01 of the AIDS Malignancy Consortium
UM1CA121947

Disclosures

Consultant:
Merck and Co
Vir Biotechnology
Virion Therapeutics
Antiva Biosciences

Speaker's honorarium
Merck and Co.

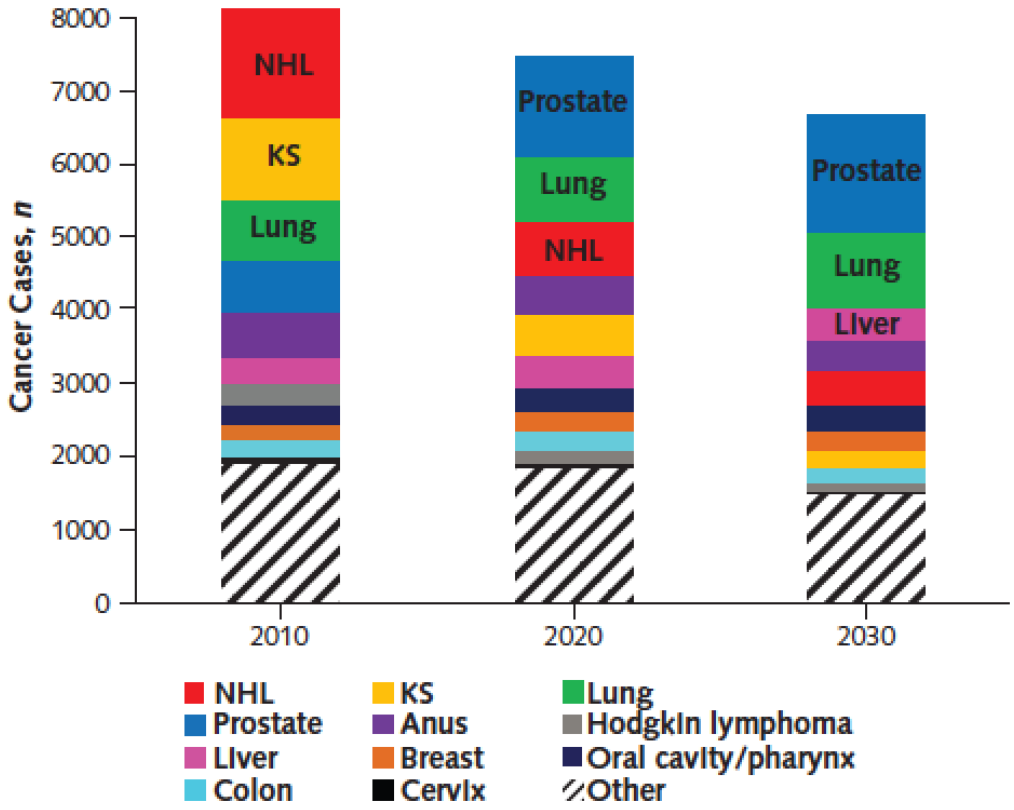
Objectives

Understand the rationale for and design of the ANCHOR Study

Understand the results of the ANCHOR Study

Discuss the implications of the ANCHOR Study

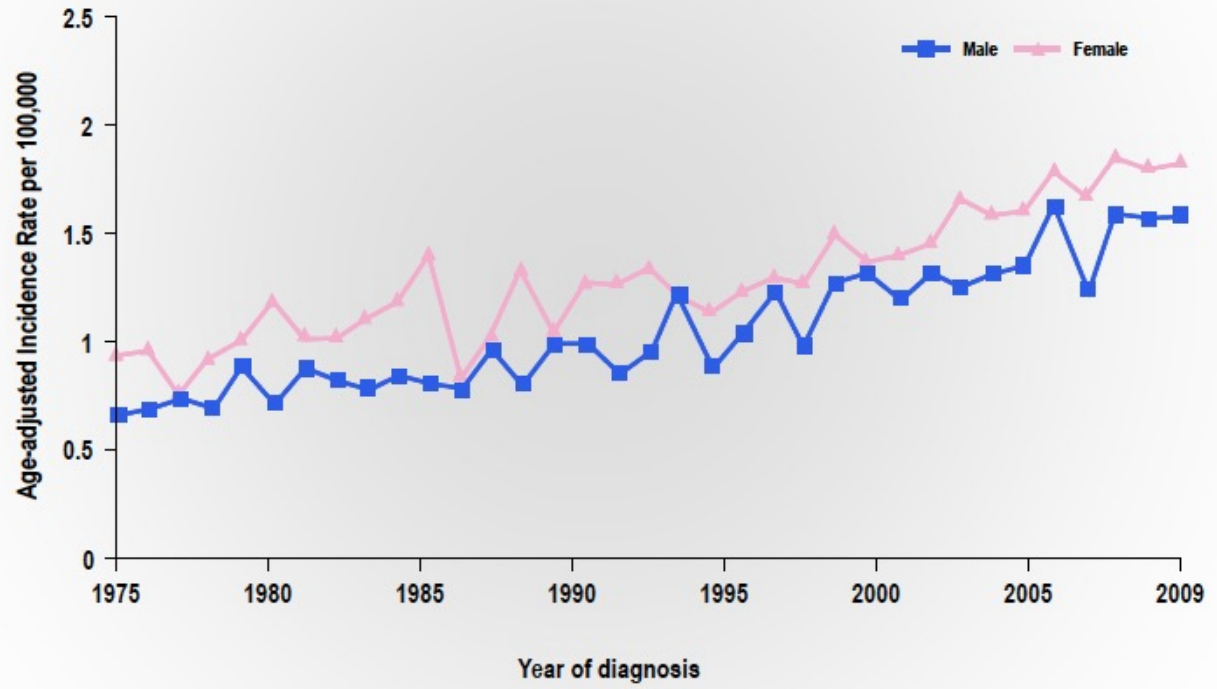
Figure 4. Estimated cancer burden (incident cancer diagnoses) among adults living with HIV in the United States, by cancer type, in 2010, 2020, and 2030.



KS = Kaposi sarcoma; NHL = non-Hodgkin lymphoma.

Shields M et al Ann Int Med 2018;168:866-873

Age-Adjusted Incidence of Invasive Anal Cancer by Gender and Year of Diagnosis: United States



Howlader N et al. (eds). SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). http://seer.cancer.gov/csr/1975_2009_pops09/. Accessed June 21, 2012.

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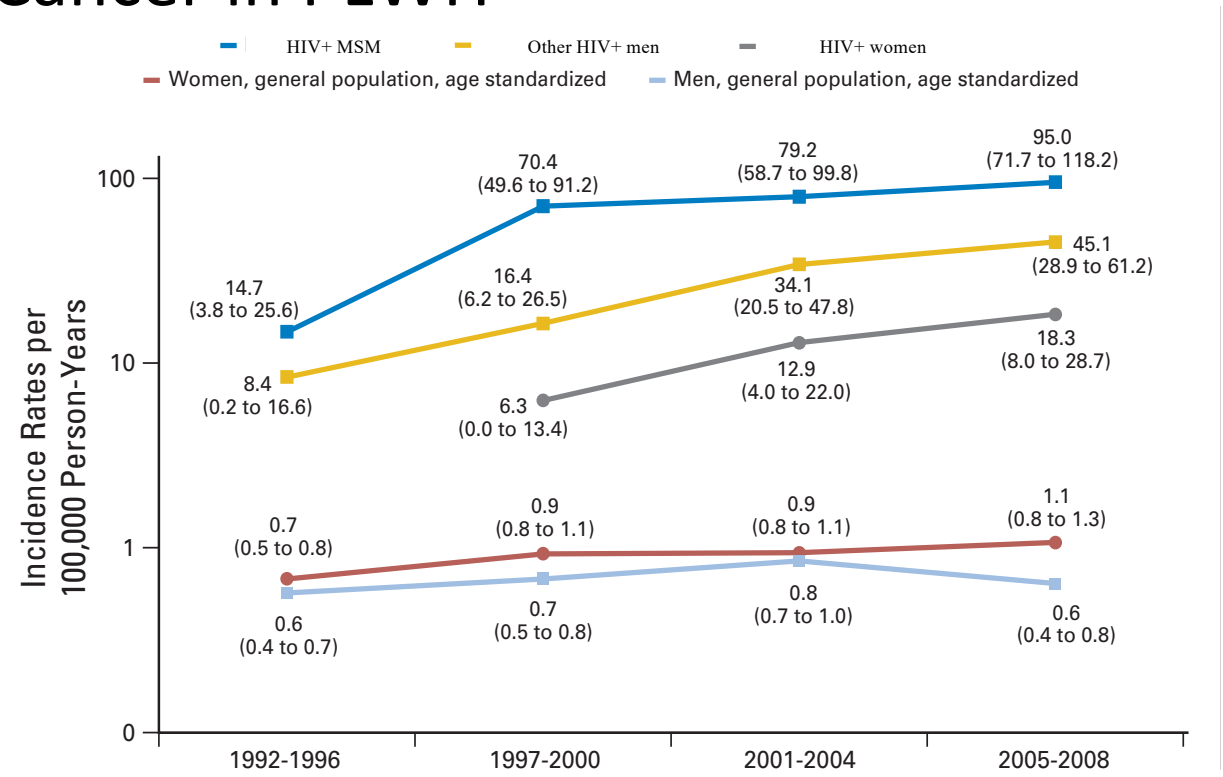
Anal cancer incidence compared to other HPV-associated cancers (US women)

Deshmukh et al. *JNCI*. 2021

Anal Cancer in PLWH



Piketty C 2012 et al. *JCO* 2012: 30(35); 4360-4366.

Recent trends in anal cancer incidence
AIDS and cancer registry match study

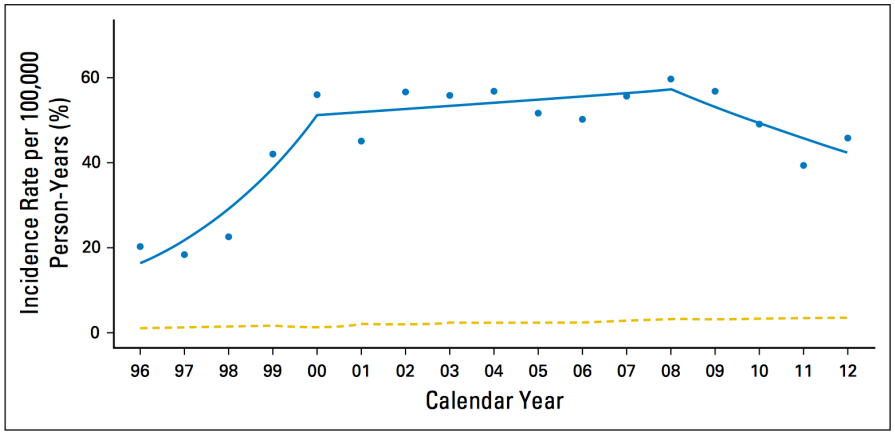


Fig 1. Trend in anal cancer incidence among people with HIV infection and the general population in the United States, 1996 to 2012. Dots indicate the observed incidence of anal cancer among people with HIV in the study population as a function of calendar year. The solid line is the model fitted by Joinpoint, with changes in slope for the incidence trend indicated in 2000 and 2008. The dashed line is the expected incidence in the general population standardized to reflect the demographic characteristics of the HIV population.

Colon-Lopez V. et al J Clin Oncol 2018; 36:68-75

Why try to prevent anal cancer?

- About 50% in the general population present with localized disease, with relatively high survival rate

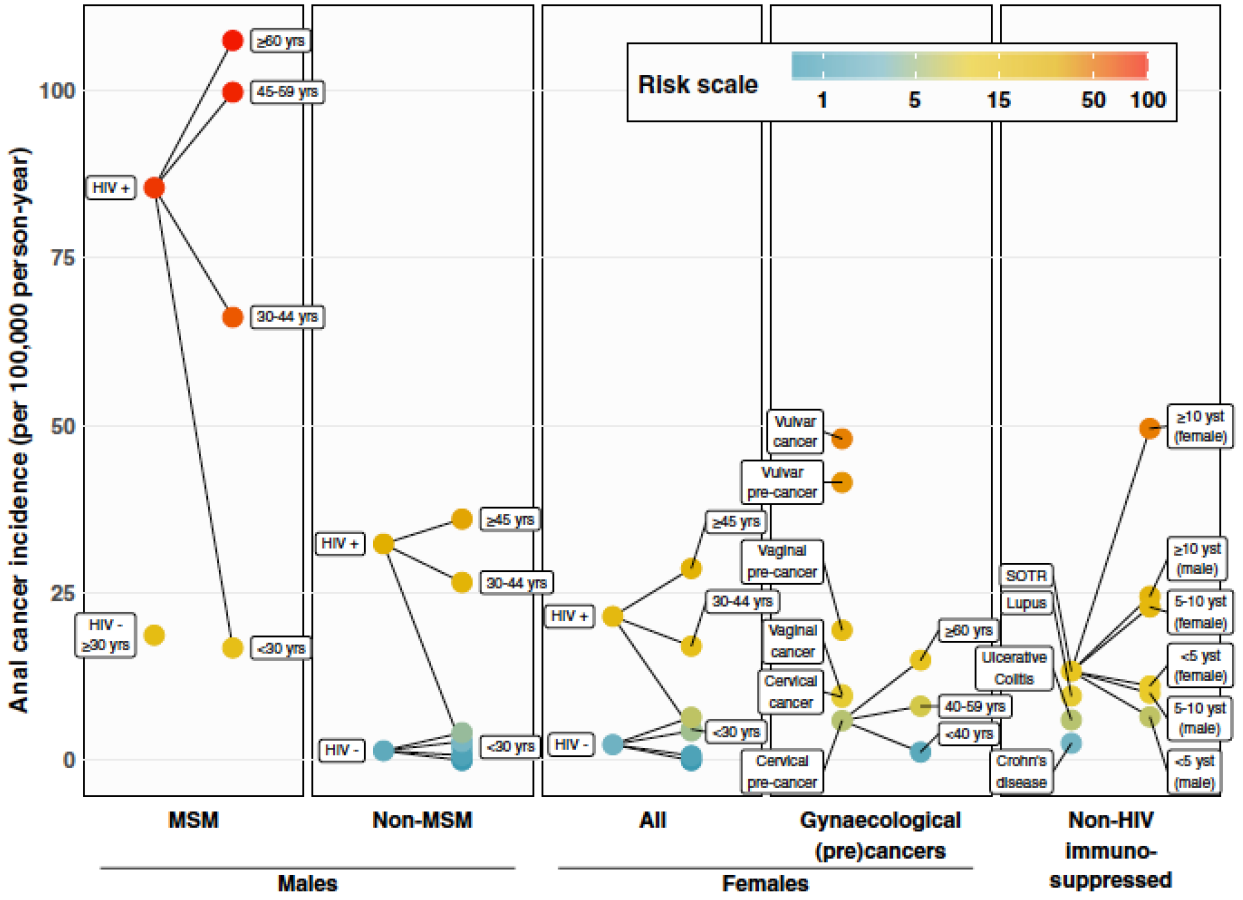
SEER stage	5-year relative survival rate
Localized	82%
Regional	66%
Distant	34%
All SEER stages combined	69%

Deshmukh A et al. J Natl Cancer Inst, 2020, Vol. 112, No. 8
Howlader N, SEER Cancer Statistics Review, 1975-2017, https://seer.cancer.gov/csr/1975_2017, posted to the SEER web site, April 2020.

Why try to prevent anal cancer?

- Survival rate is lower for more advanced disease
- Among those who do survive, there is substantial morbidity associated with standard treatment, primarily due to radiation therapy

Anal cancer risk scale



Clifford et al. Int. J. Cancer. 2020;1–11. https://doi.org/10.1002/ijc.33185

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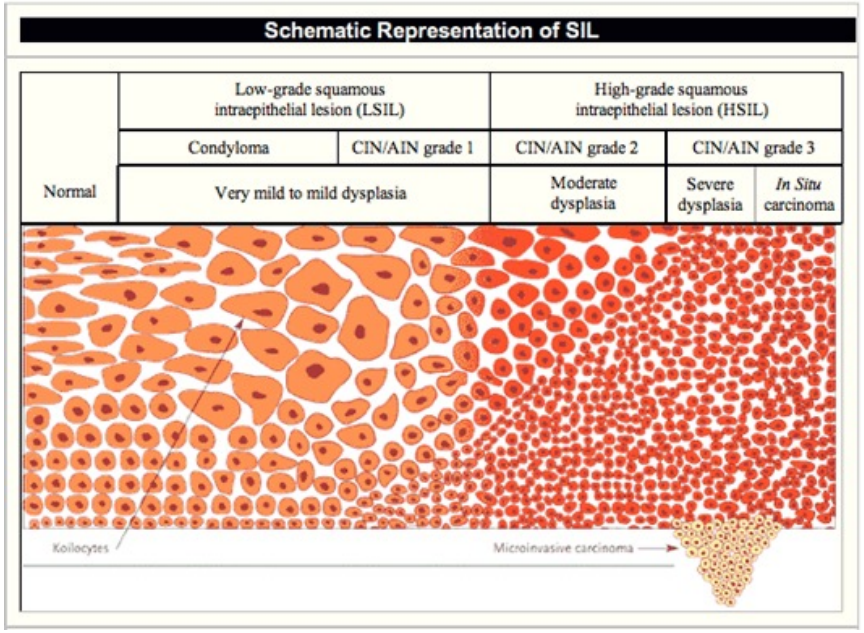
The cervical model

Anal and anal cancer are very similar diseases
Cervical cancer and anal cancer are preceded by high grade squamous intraepithelial lesions (HSIL)



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The cervical model of cancer prevention

Treatment of cervical HSIL is proven to reduce the incidence of cervical cancer
Why do we not routinely screen for and treat anal HSIL?

Lack of evidence that it will work

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Why anal screening and treatment of HSIL might not work

- In many at-risk people lesions are large and multifocal
- Clinicians may miss lesions
- Clinicians may inadequately treat lesions
- New lesions often arise- anal whack-a-mole!

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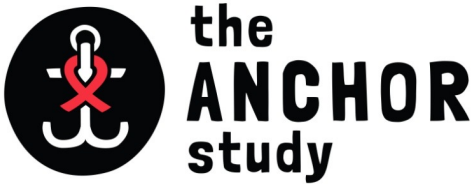
Aim 1: To determine whether treating anal high-grade squamous intraepithelial lesions (HSIL) is effective in reducing the incidence of anal cancer in PLWH

Aim 2: To determine the safety of treatment for anal HSIL

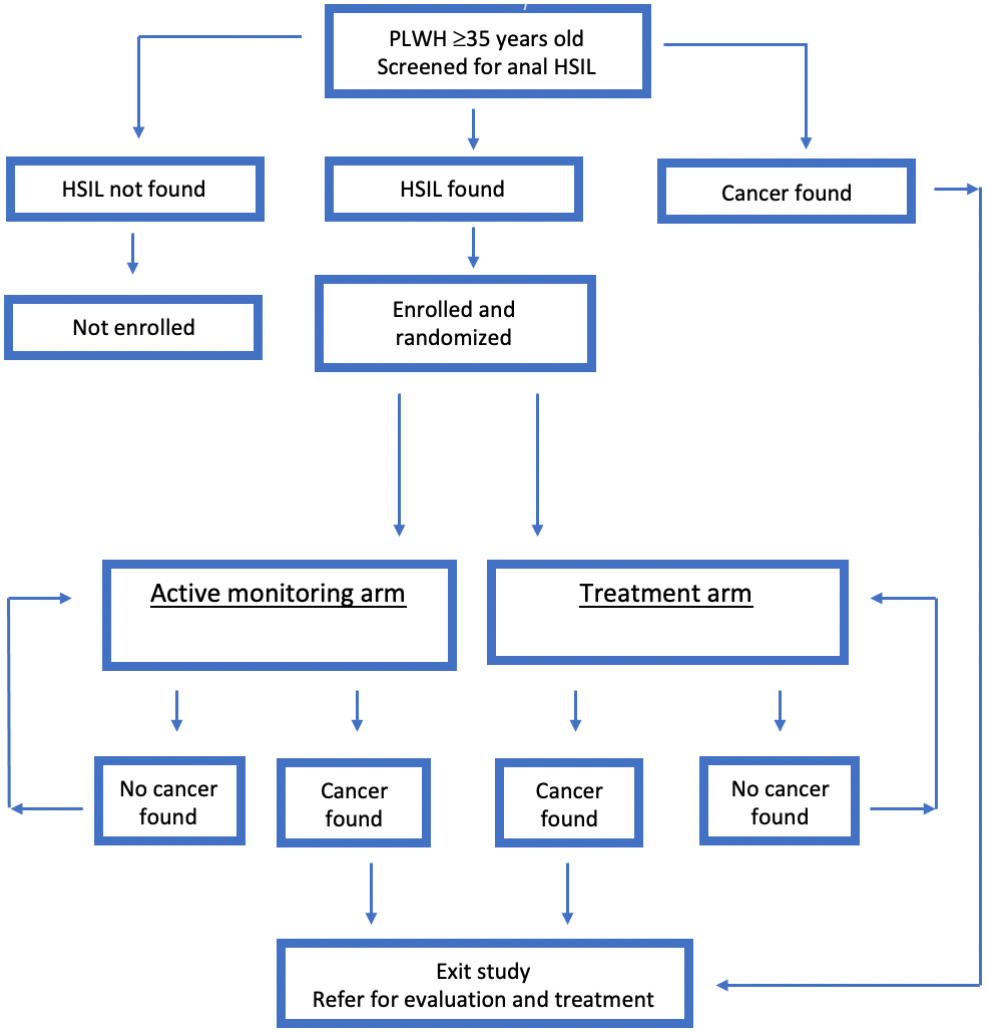


Aim 3: To develop and implement an instrument to measure the impact of ANCHOR procedures on QoL (ANCHOR Health-Related Symptom Index (A-HRSI)

Aim 4: Collect clinical specimens and data to create a bank of well-annotated specimens that will enable correlative science:
Identify host and viral factors in HSIL progression to cancer
Identify host and viral biomarkers of progression from HSIL to cancer

Study schema

Enroll 5,058



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A study of the AIDS Malignancy Consortium
Funded by the National Cancer Institute

Methods

- Powered to detect difference between 50/100,000 PY in the treatment arm and 200/100,000 PY in the AM arm at the two-sided 0.05 significance level with power of 0.90
- Event-driven analysis, primary outcome= time-to-cancer
- N=2,529 per arm (total 5,058) to detect 31 anal cancers

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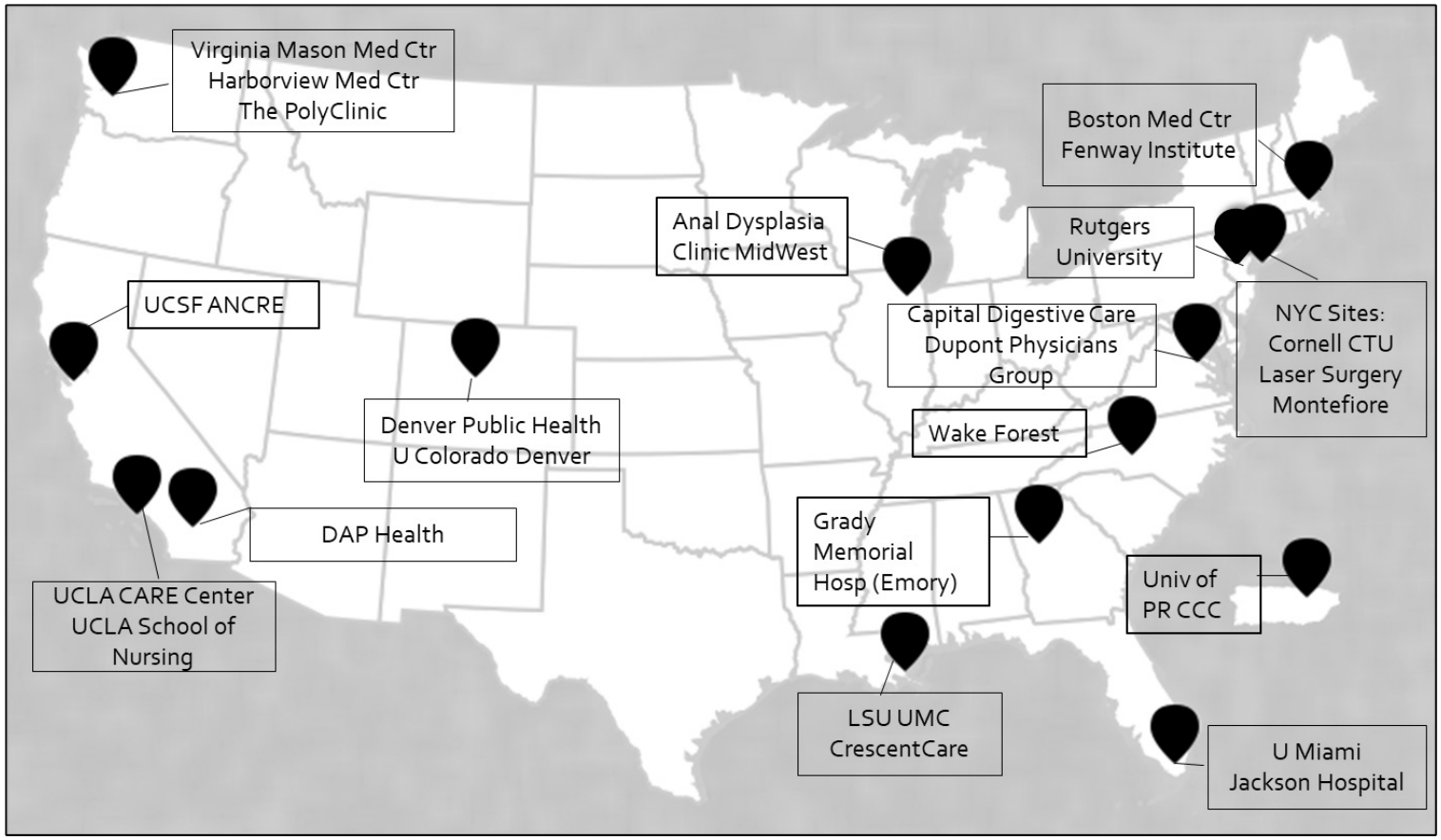
ANCHOR sites



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Methods- screening

- Informed consent
- Phlebotomy
- Anal swabs for cytology and other testing
- High resolution anoscopy with biopsy

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Methods- randomization

- If screening biopsy= HSIL and otherwise eligible, participant returned for randomization
- Questionnaire detailing medical history, lifestyle information
- Randomization stratified by:
  - study site
  - nadir CD4 count ($\leq$200 cells/mm^3, $>$ 200 cells/mm^3)
  - lesion size at randomization ($\leq$50% of anal canal/perianal region, $>$50% of anal canal/perianal region)

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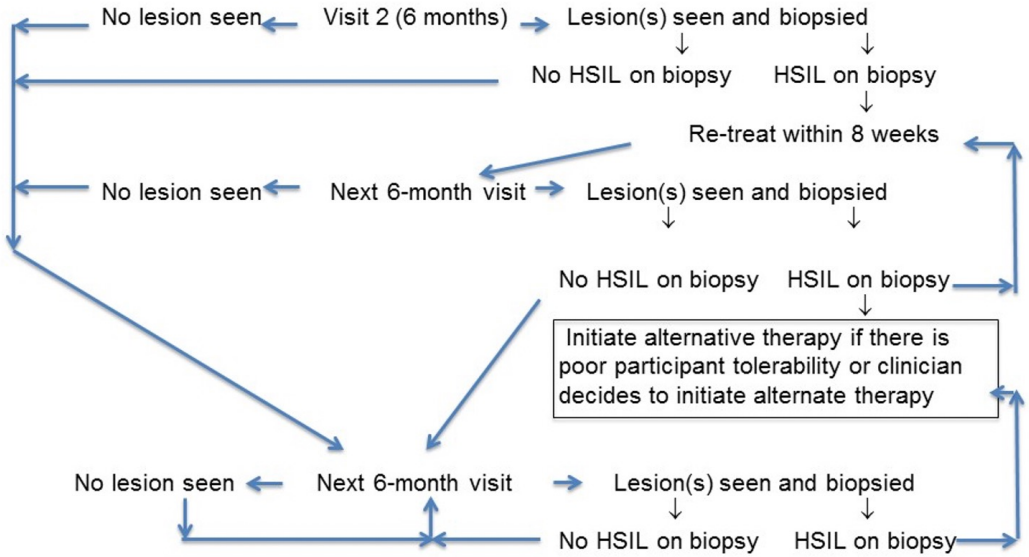
Treatment arm

- Treated immediately- hyfrecation, IRC, 5-FU, imiquimod

Figure 4-B: IRC, hyfrecation, or electrocautery performed at visit 1 (randomization visit)



If no lesions are seen, participant will return for HRA at the next 6 month visit. If HSIL is found, alternative treatment is initiated per guidelines

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Treatment arm

- Followed according to treatment algorithm
- Biopsied if suspicion for HSIL
- Anal cytology, swabs, HRA, blood every 6 months after HSIL cleared
- Every 3 months if concern for cancer
- Biopsied at any visit if concern for cancer

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Active monitoring arm

- Anal cytology, swabs, HRA, blood every 6 months
- Biopsied annually to confirm persistent HSIL
- Every 3 months if concern for cancer
- Biopsied at any visit if concern for cancer

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Screening

- 10,723 PLWH from 9/24/2014 to 8/5/2021
  - 52.2% had biopsy-proven anal HSIL
  - 53.3% of men
  - 45.8% of women
  - 62.5% of transgender individuals
- 17 individuals (0.16%, 160/100,000) were diagnosed with anal cancer

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Demographics of randomized population (1)

	Randomized population N=4,446		P value
	Treatment arm	Active monitoring arm	
	N=2,227	N= 2,219	
Median age at randomization (years, IQR)	51.0 (44.0-57.0)	51.0 (44.0-57.0)	0.79
Median years at randomization since HIV diagnosis (years, IQR)	17.0 (10.0-24.0)	17.0 (10.0-25.0)	0.96
Months of follow-up (median, IQR)	25.3 (11.7 – 42.0)	27.2 (12.0 – 42.1)	0.77
Gender identity N (%)			0.30[2]
Male	1793 (80.5)	1782 (80.3)	
Female	346 (15.5)	365 (16.5)	
Transgender	85 (3.8)	68 (3.1)	
Neither male nor female	2 (0.1)	2 (0.1)	
Decline to answer	1 (0.0)	2(0.1)	

Demographics of randomized population (2)

	Randomized population N=4,446		P value
	Treatment arm	Active monitoring arm	
	N=2,227	N= 2,219	
Race/ethnicity N (%)			
Non-Hispanic White	695 (31.2)	737 (33.2)	0.37
African-American	935 (42.0)	939 (42.3)	
Hispanic, non-African-American	381 (17.1)	339 (15.3)	
Asian/Pacific Islander	27 (1.2)	29 (1.3)	
Other/Unknown	189 (8.5)	175 (7.9)	
CDC HIV risk group N (%)			
Homosexual	1738 (78.0)	1742 (78.5)	0.74
Heterosexual	532 (23.9)	510 (23.0)	0.48
Injection drug use	152 (6.8)	177 (8.0)	0.14
Transfusion	53 (2.4)	47 (2.1)	0.56
Hemophilia	2 (0.1)	4 (0.2)	0.41
Other high-risk group	34 (1.5)	27 (1.2)	0.37

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Demographics of randomized population (3)

	Randomized population N=4,446		P value
	Treatment arm	Active monitoring arm	
	N=2,227	N= 2,219	
Current smoker N (%)	710 (31.9)	743 (33.5)	0.26
Plasma HIV-1 RNA copies/mL at randomization N (%)			0.27
<50	1852 (83.7)	1800 (81.8)	
51-199	155 (7.0)	160 (7.3)	
200-1000	83 (3.8)	93 (4.2)	
>1000	122 (5.5)	148 (6.7)	
CD4 cells/uL at randomization (median, IQR)	602 (393-827)	607 (410-837)	0.32

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Demographics of randomized population (4)

	Randomized population N=4,446		P value[1]
	Treatment arm	Active monitoring arm	
	N=2,227	N= 2,219	
Stratification factors at randomization N (%)			
Nadir CD4 cells/uL			0.88
≤200 cells/uL	1130 (50.7)	1121 (50.5)	
>200 cells/uL	1097 (49.3)	1098 (49.5)	
HSIL size at screening			0.93[8]
>50% of anal canal/perianal region	285 (12.8)	282 (12.7)	
≤50% of anal canal/perianal region	1942 (87.2)	1937(87.3)	

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Results

For the participants in the treatment arm, initial treatment:
Office-based electrocautery ablation (92.9%)
Infrared coagulation (5.6%)
TUA (4.6%)
Topical 5-fuorouracil cream (7%)
Topical imiquimod (1.2%)

Over the course of the study:
1921 (86.0%) with therapeutic modality
233 (10.4%) with two modalities
33 (1.5%) with three modalities
1 (<0.1%) with four modalities

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Results

DSMB notified when 32 cancers diagnosed
final analysis based on 30 cases
9 participants were diagnosed with invasive anal cancer in the treatment arm and 21 in the AM arm
Median follow-up of 25.8 months, 57% reduction in anal cancer (95% CI 6% to 80%, chi-squared = 4.74, P=.029)
Cancer incidence in the treatment arm was 173/100,000 PY of follow-up, compared with 402/100,000 PY in the AM arm

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Kaplan-Meier curve of time-to-confirmed cancer cases

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Results

- DSMB recommended stopping the study for efficacy
- Recommendation made to treat all individuals in the monitoring arm
- We will continue to follow all individuals who wish to be treated and/or followed

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- 73 year old male living with HIV
- CD4 nadir <200, current CD4 504, VL ND, no OIs

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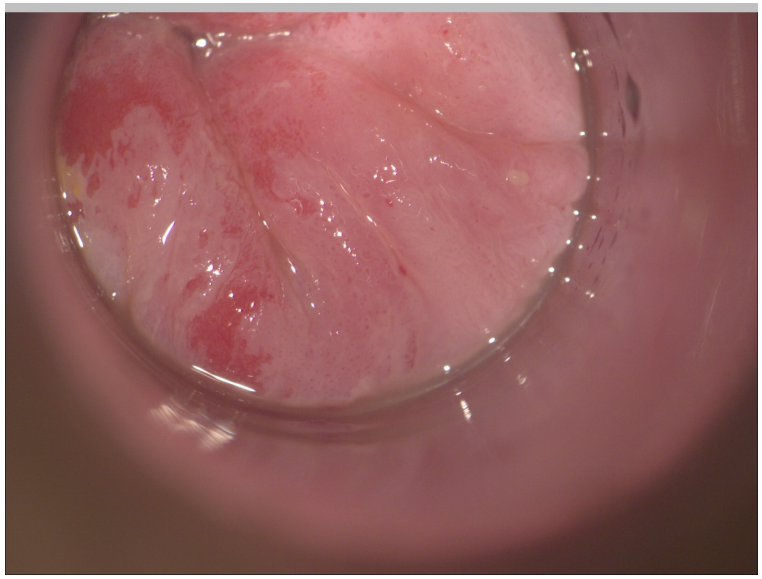
Visit 1 5/16



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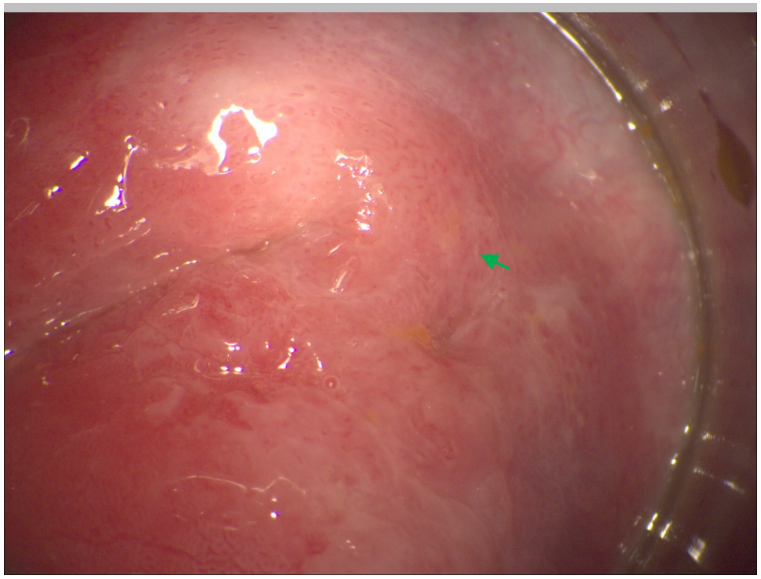

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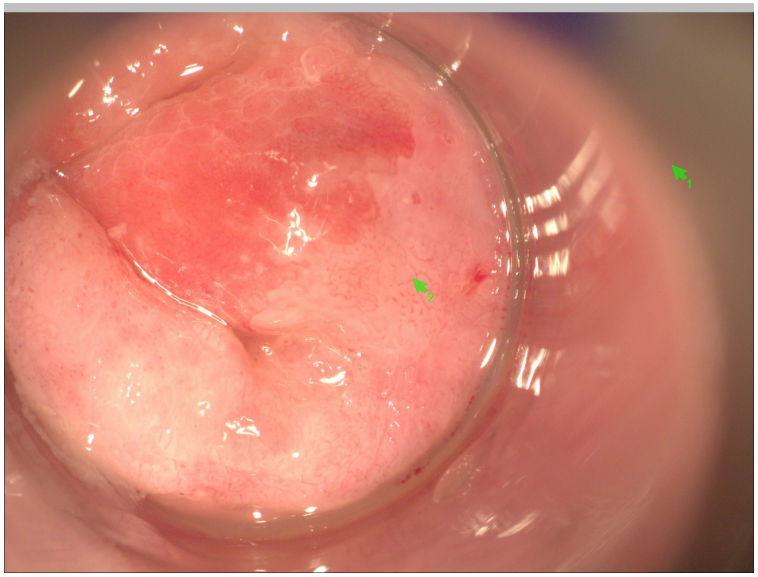

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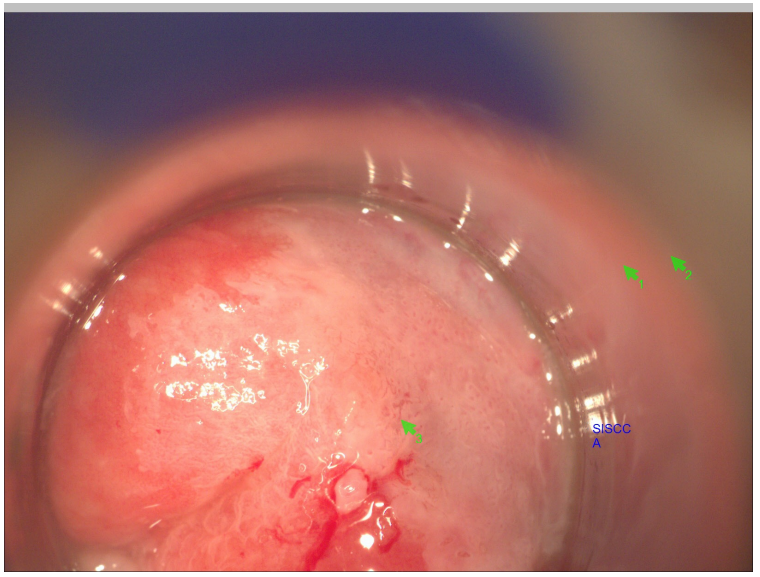

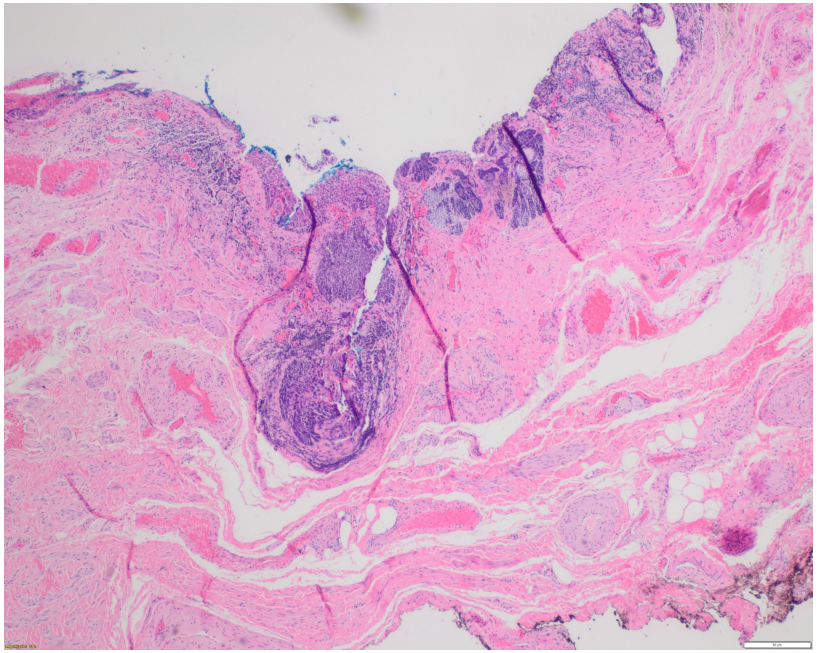

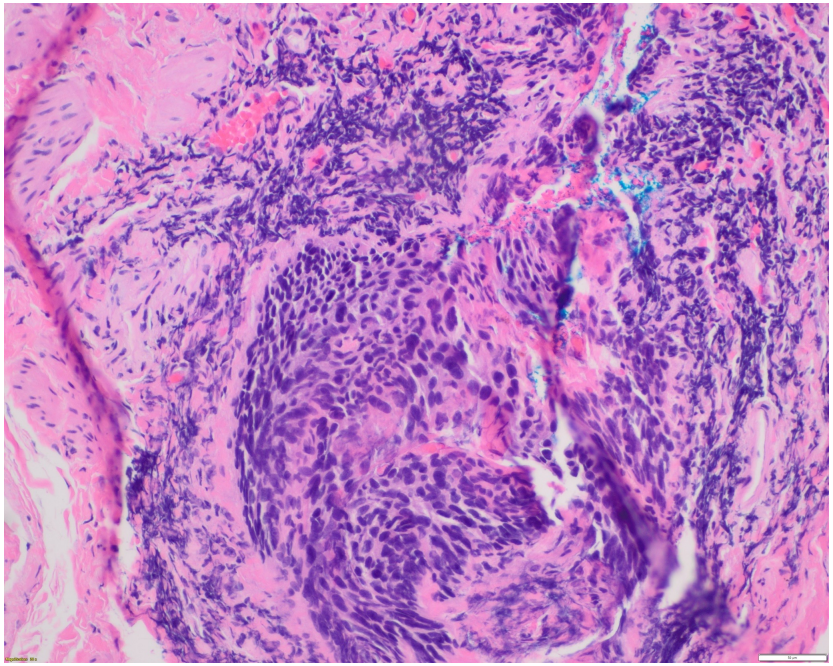

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- 37 yo male
- Nadir CD4 54, current CD4 429; VL ND
- H/O intra anal condyloma in 2014 treated with laser

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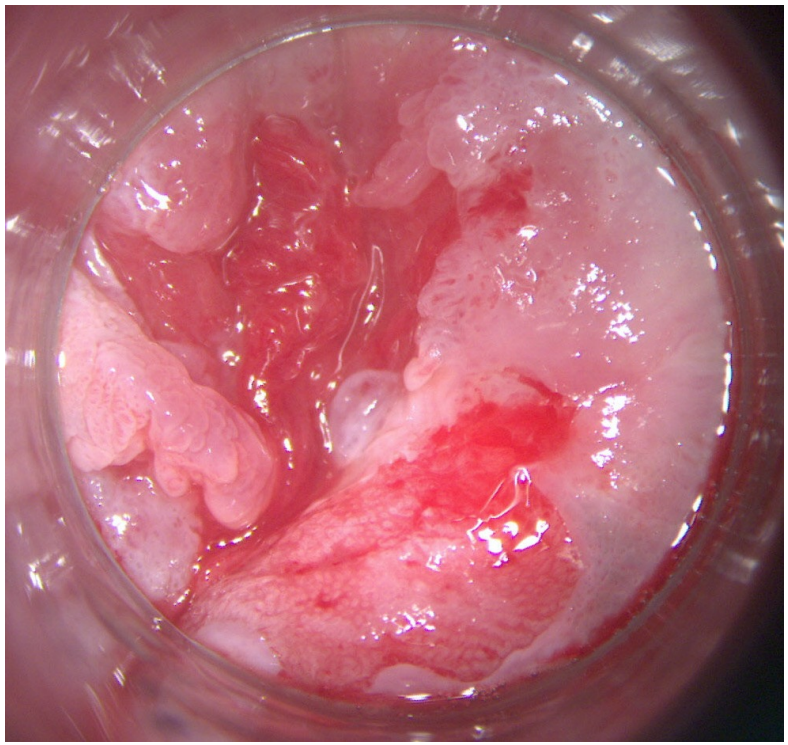
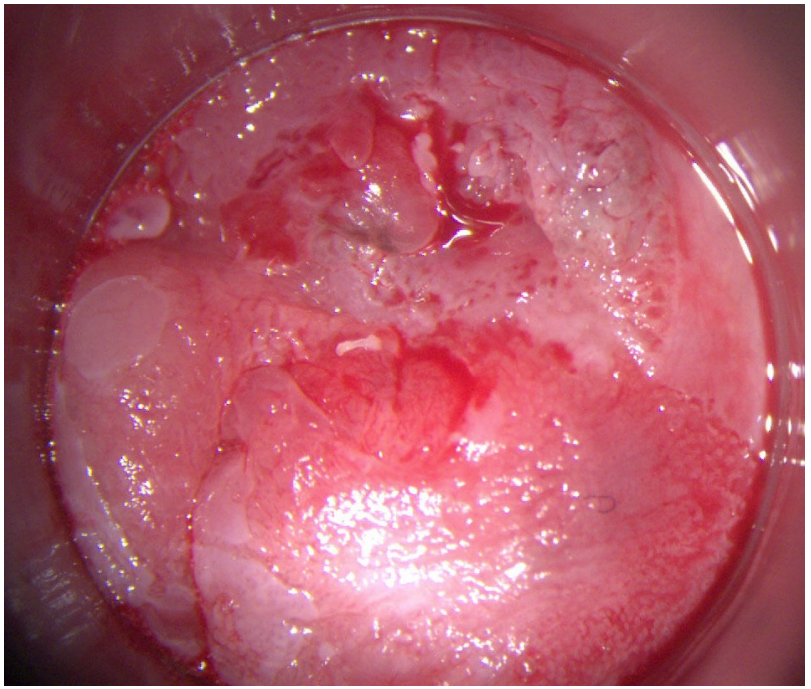
Screening 11/17 Visit 4 06/19





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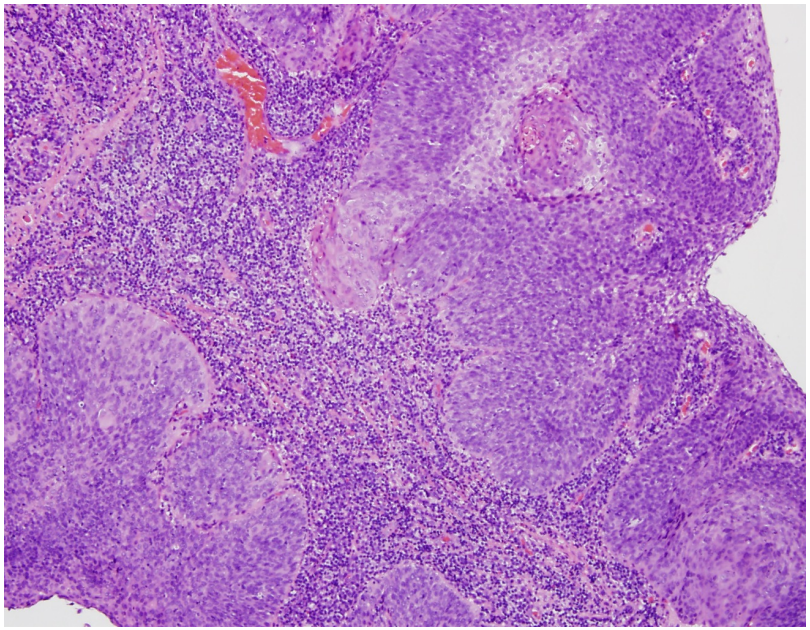
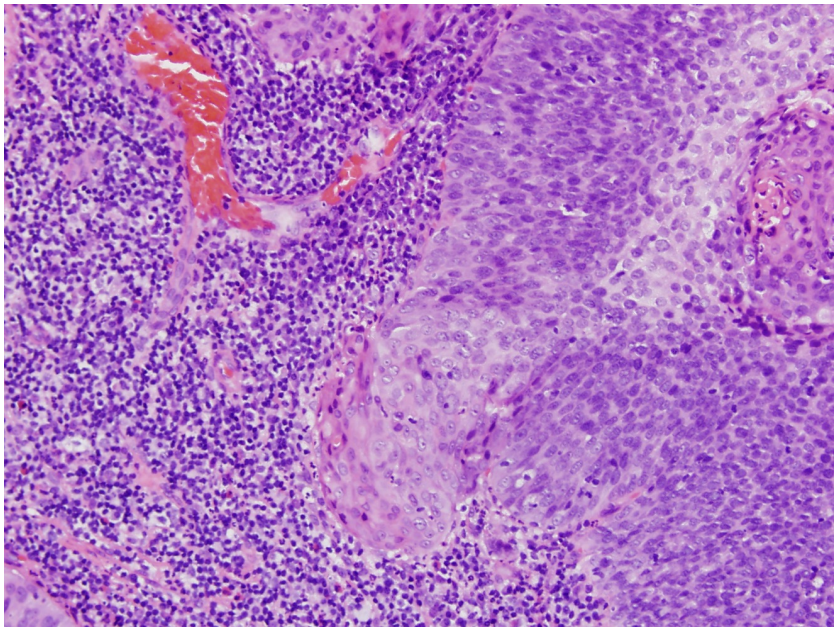
Histopathology





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Adverse events

	Treatment arm	Active monitoring arm
Adverse events (N)	683	635
Deaths	54	48
Serious adverse events (N)	586	568
Study-related adverse events (N)	43	4
Study-related serious adverse events (N)	7	1
Skin ulceration due to 5-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

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Implications of the study findings

- Treatment of anal HSIL is effective in reducing the incidence of anal cancer
- These data should be included in an overall assessment for inclusion of screening for and treating anal HSIL as standard of care

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Implications of the study findings

- There is room for improvement in treatment of anal HSIL
- There is a need for biomarkers for HSIL progression or regression

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Implications of the study findings

- There is a need for optimization of screening algorithms for HSIL
- There is a need for a large scale-up of HRA training programs
- Extrapolation of our results to other groups at high risk of anal cancer

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With deep gratitude to:

- ANCHOR Investigators Group and the study staffs at all of the ANCHOR sites
- Study participants
- ANCHOR Community Advisory Board
- AIDS Malignancy Consortium
- Emmes Corporation
- NCI/Office of HIV and AIDS Malignancies

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Thank You for Your Attendance!
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