Anal Cancer Screening

Please feel free to ask questions throughout the presentation!

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Appreciation and Disclosures

A BIG thank you to Dr. Jeff Schouten for all his work in anal cancer prevention, for training me in high resolution anoscopy (HRA), and providing these slides.

No disclosures

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Outline

- What We Know About Anal cancer
- Who Is at Risk for Anal Cancer
- HPV Induced Dysplasia
- ANCHOR study
- Screening Guidelines
- How to Screen: DARE & Anal Pap
- High Resolution Anoscopy Basics
- HSIL & Condyloma Treatment Options
- HPV Vaccination
- Future Directions

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What We Know About Anal Cancer

- 10,000 cases of anal cancer yearly in the US, over 50,000 globally
- 27th most common cause of cancer in the US
- Anal cancer rates are rising in the general population and in people living with HIV despite HAART
- People living with HIV have significantly higher rates of anal cancer
- Overall increased risk of cancer in PLWH is 1.5-2 fold higher than general population
- Anal cancer is preceded by high-grade squamous intraepithelial lesions (HSIL) caused by HPV

anchorstudy.org; Hayden S Andrews, Meena Murthy, Benjamin T Davis, State-of-the-Art Review: Anal Cancer Screening in People With HIV, *Clinical Infectious Diseases*, Volume 80, Issue 6, 15 June 2025, Pages e80–e88, https://doi.org/10.1093/cid/ciaf073

Other Known Risk Factors for Anal Cancer

- **Infection with oncogenic strains of HPV (i.e., HPV 16 and 18**
- History of having a low CD4+ cell count (nadir CD4)
- Receptive anal sex
- Other defects in cell mediated immunity including immunosuppressive medications
- Cervical and vulvar HSIL and cancers
- History of genital warts (condyloma)
- Smoking
- Older age

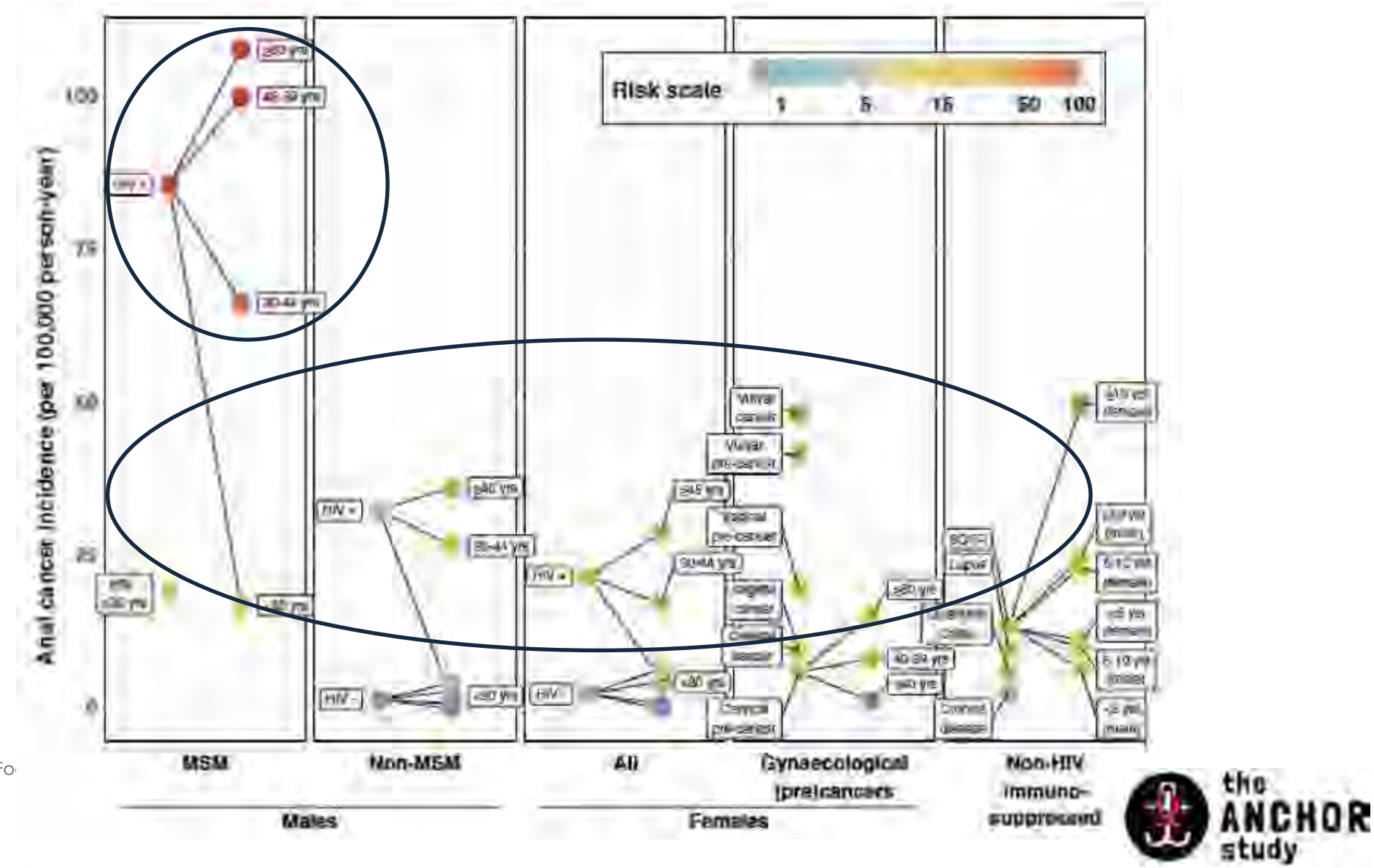
Anal Cancer Incidence: General population

1.7/ 100,000 persons

MSM and [redacted] living with HIV age 35+	[illegible]
Vulvar cancer, VIN3	>40
MSW LWH age 45+	40
Women LWH age 45+	25
Solid organ transplant recipients, 10 yrs post-transplant	>25
MSM and [redacted] without HIV age 45+	>18

ASCCP Practice Advisory: Anal Cancer Screening; Table 1 based on Clifford et al. *Int J Cancer* 2021.

Anal cancer risk scale



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

HPV (Human Papillomavirus)

- Most common sexually transmitted infection in the world
- Lifetime risk for anogenital HPV infection is 80-90%
- Over 100 types, approximately 15 are oncogenic (types 16, 18, and others)
- Causes squamous cell adenocarcinoma at various anatomical sites
- Found in 90% of cervical and anal cancers, up to 70% of oropharyngeal cancers, most penile, vulvar, vaginal cancers

Saraiya M, J Natl Cancer Inst. 2015 Apr 29;107(6):djv086.

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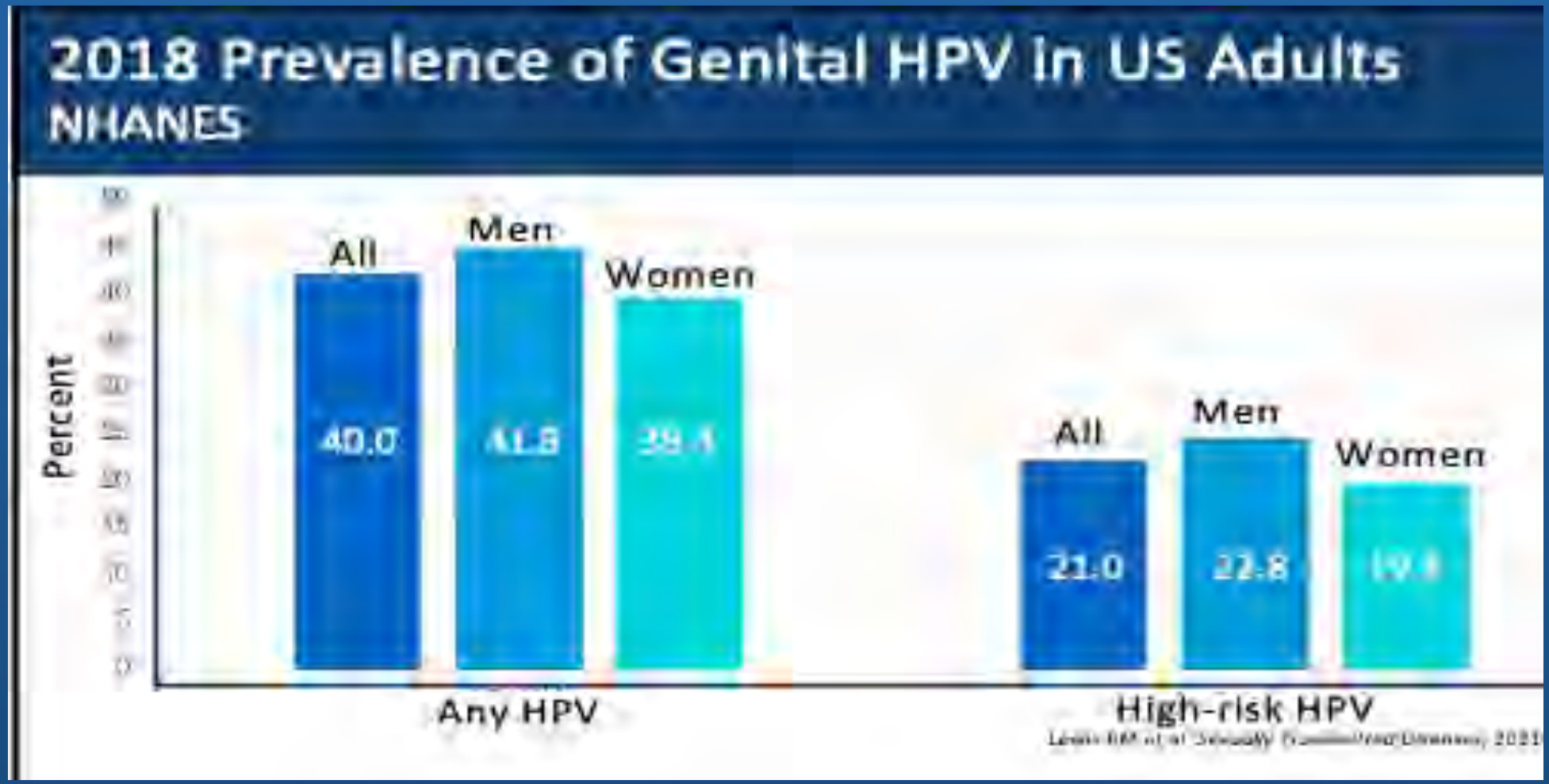
HPV Prevalence- General Population



Slide from General HPV Epidemiology, Christina Brickman, MD, IANS HRA Course 2024.

Anal HPV Prevalence in People Living with HIV

> 70% for MSM

> 25% for MSW

16%–85% for women- most studies show higher incidence than cervical HPV infection

Hayden S Andrews, Meena Murthy, Benjamin T Davis, State-of-the-Art Review: Anal Cancer Screening in People With HIV, *Clinical Infectious Diseases*, Volume 80, Issue 6, 15 June 2025, Pages e80–e88, https://doi.org/10.1093/cid/ciaf073

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HPV Causes Anal Dysplasia

- Dysplasia- the presence of abnormal cells within a tissue or organ
- Low Grade Squamous Intraepithelial Lesion (LSIL)
  - Generally does not progress into cancer
  - For example- anal condylomas
- High Grade Squamous Intraepithelial Lesion (HSIL)
  - Precedes anal cancer
  - Caused by HPV types 16, 18 and others

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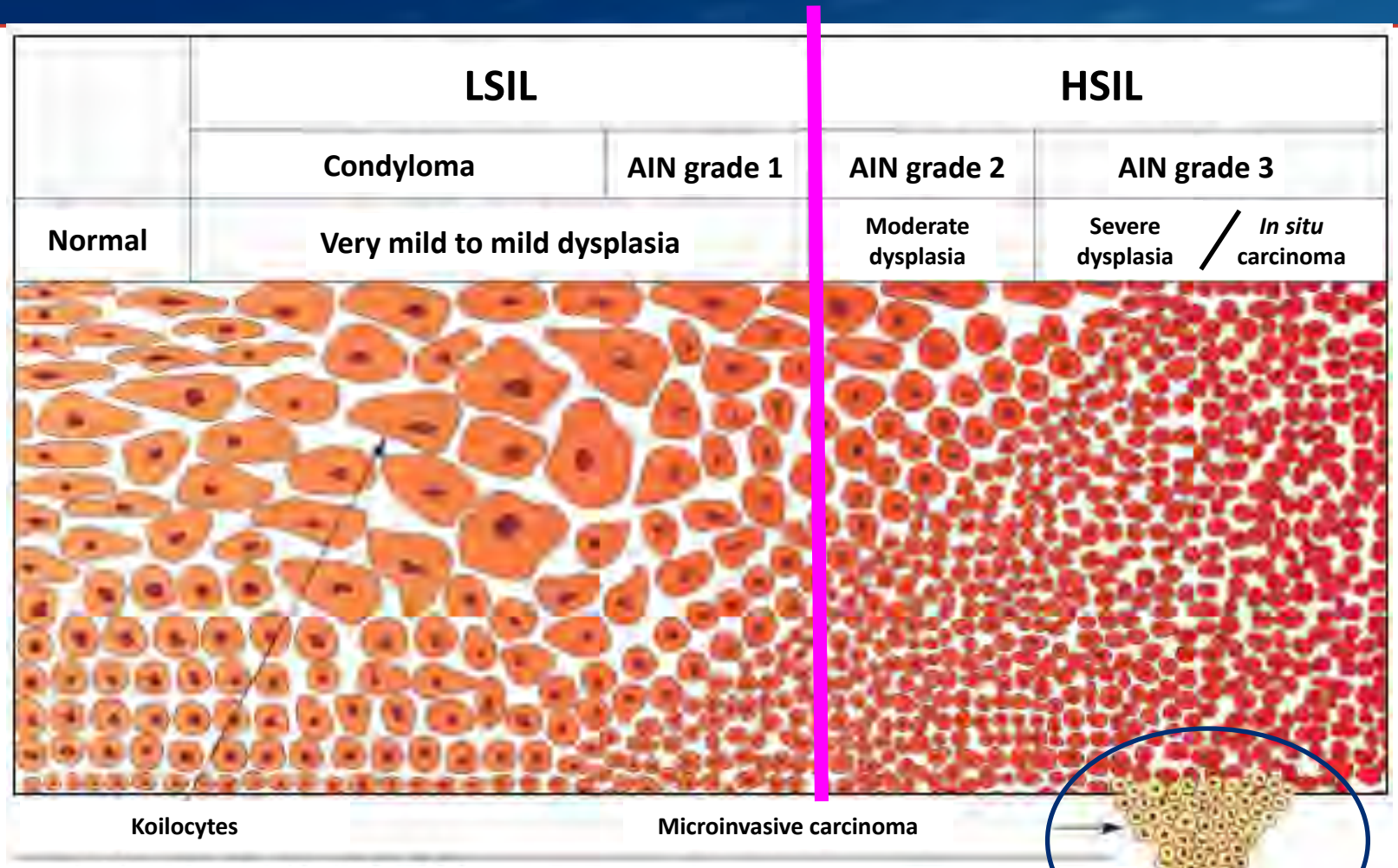
HPV-induced Anal Dysplasia



With increasing severity of SIL of the 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 HSIL, as depicted in the drawing by epithelial cells crossing the basement membrane below the region of HSIL.

Journal of Lower Genital Tract Disease, Volume 16, Number 3, 2012, 205-242

Cytology vs Histology

-Same terms used to describe dysplasia (LSIL and HSIL)

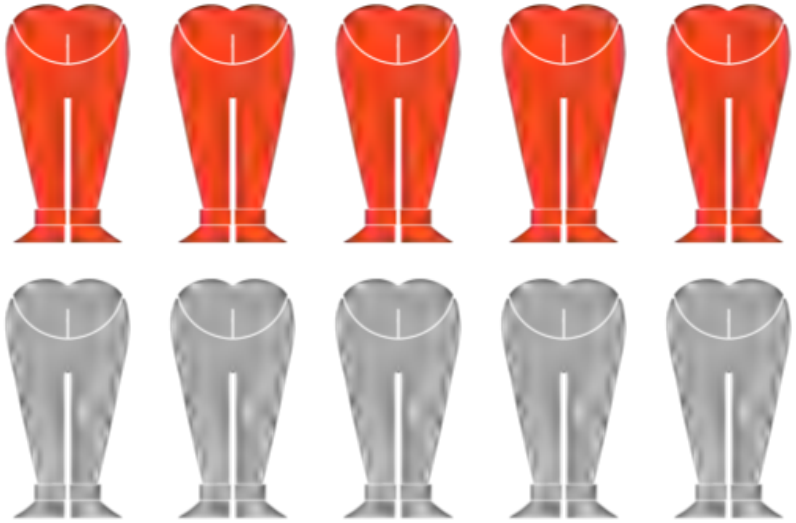
-50% or more of highest risk groups (ie MSM living with HIV) with LSIL or ASCUS on pap will have HSIL on histology (biopsy)

-LSIL will not precede cancer but is a risk factor for histologic HSIL

-We may be missing the anal transition zone?

Hayden S Andrews, Meena Murthy, Benjamin T Davis, State-of-the-Art Review: Anal Cancer Screening in People With HIV, *Clinical Infectious Diseases*, Volume 80, Issue 6, 15 June 2025, Pages e80–e88, https://doi.org/10.1093/cid/ciaf073

Among MSM living with HIV, 5 Out of 10 Asymptomatic Men Have Anal HSIL



Among Women Living with HIV, It Is Estimated That 2 Out of 10 Have Anal HSIL

About 1 In 10 MSM Living With HIV Will Get Anal Cancer Over Their Lifetime

Anchorstudy.org

It is Not Known How Many Women Living with HIV Will Get Anal Cancer

Why try to prevent anal cancer?

- About 50% in the general population present with localized disease, with relatively high survival rate
- Survival rate is lower for more advanced disease
- Substantial morbidity associated with standard treatment, primarily due to radiation therapy

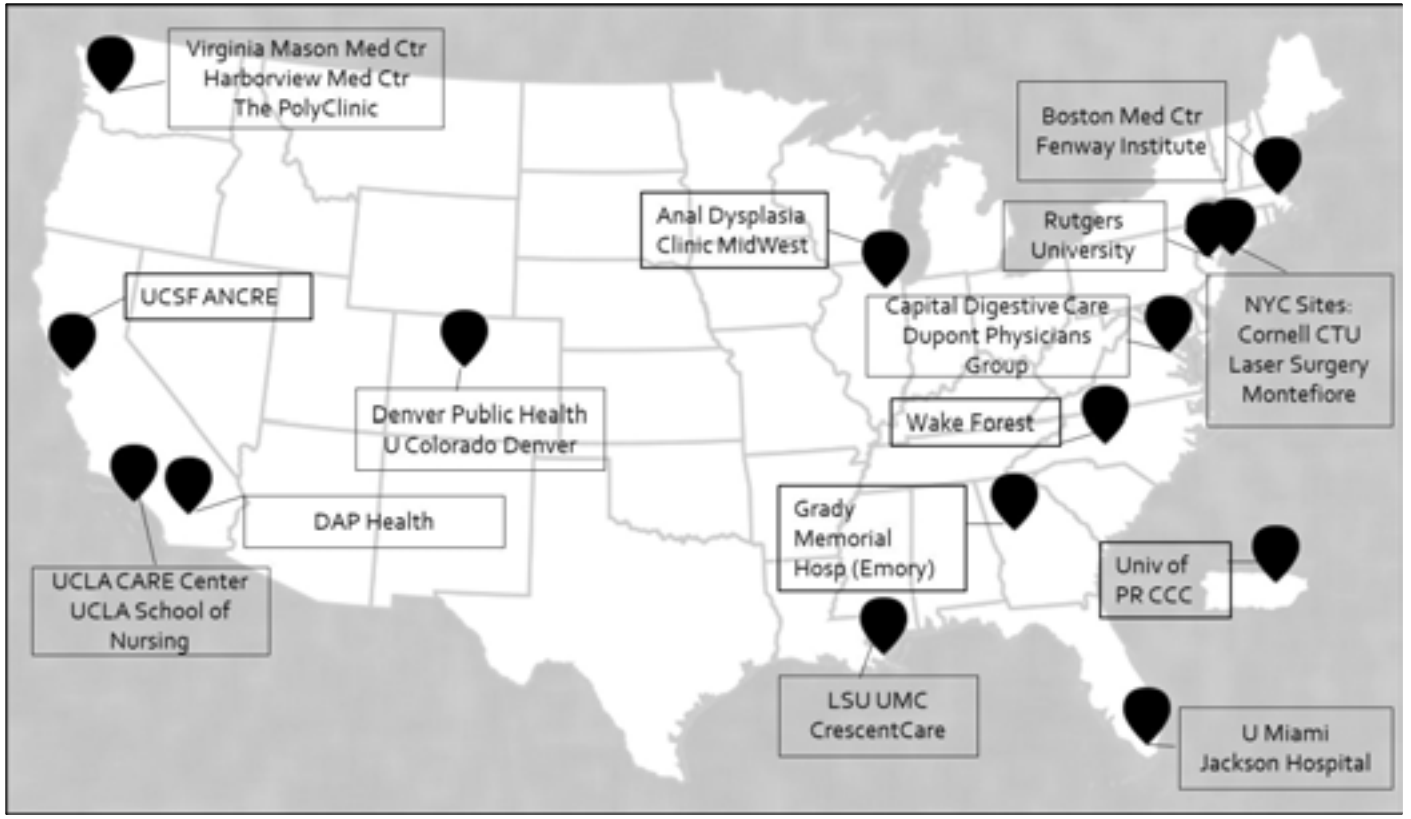
SEER stage	5-year relative survival rate
Localized	82%
Regional	66%
Distant	34%
All SEER stages combined	69%

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.

the ANCHOR study


the
ANCHOR
study

ANCHOR sites



the ANCHOR study

Large, phase 3 RCT lead by researchers at UCSF with 21 clinical sites

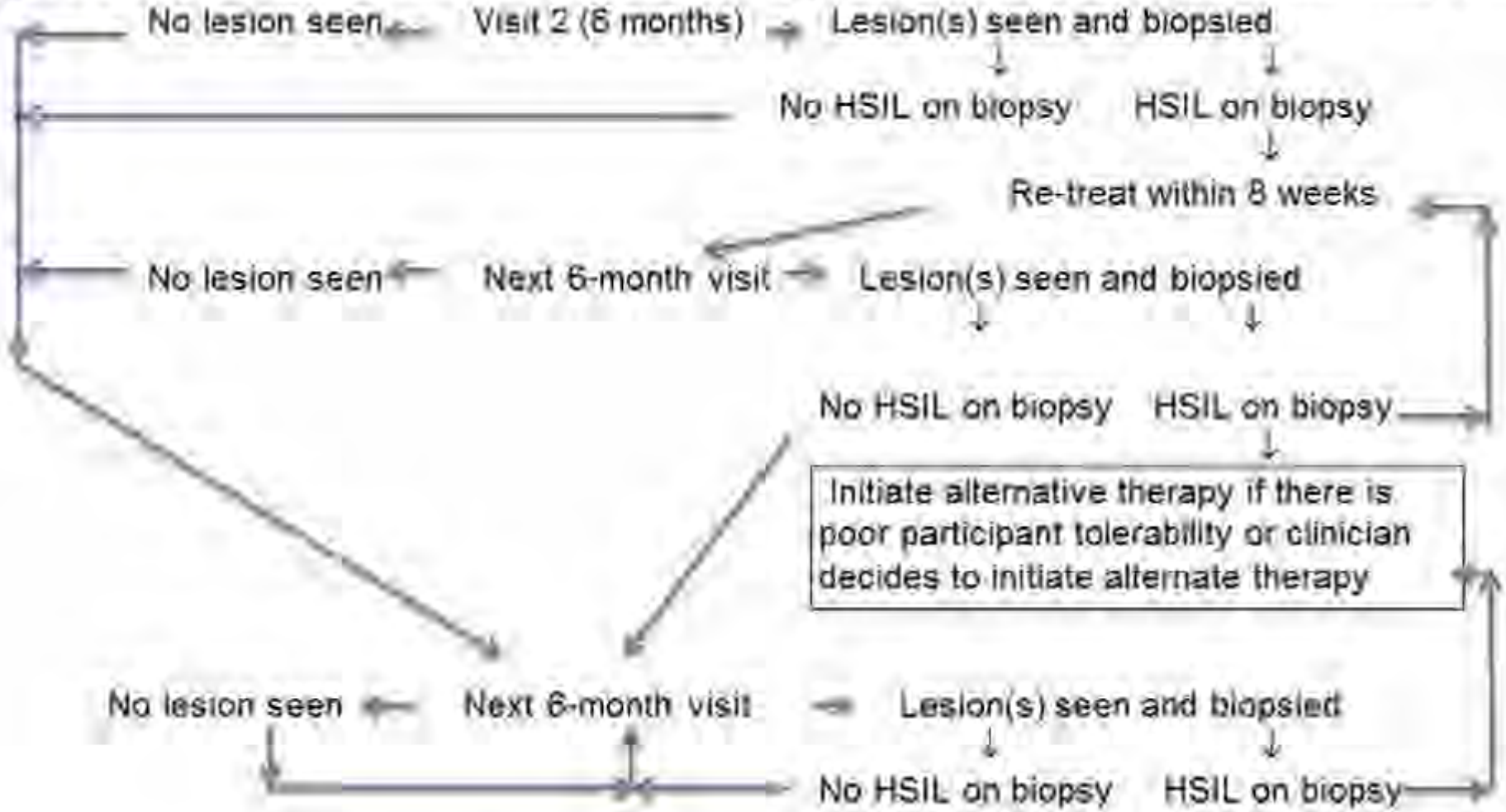
The ANCHOR Study

Is treating anal high-grade squamous intraepithelial lesions (HSIL) effective in reducing the incidence of anal cancer in PLWH?

The ANCHOR Study

- 4,446 patients enrolled in 5 year study
  - 80% men
  - ~80% virologically suppressed
  - Median age 51
  - Median CD4 count 600 cells/mm^3
- Patients living with HIV ages 35 and older with HSIL randomized into treatment or active monitoring
- Monitored every 3-6 months
- Stratified for nadir CD4 count and HSIL size < or > 50% of anal canal/perianal region

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

	Treatment Arm	Active Monitoring Arm
Biopsy	If suspicion for HSIL At any visit if concern for cancer	Annually to confirm persistent HSIL At any visit if concern for cancer
Anal cytology, swabs, HRA, blood	q6 months after HSIL cleared	q6 months
Visit	Every 3 months if concern for cancer	

the ANCHOR study

ANCHOR Results

- Data Safety and Monitoring Board notified when 32 cancers diagnosed (incident cases)
  - Final analysis based on 30 cases
  - Stopped for efficacy October 2021
  - Recommended treatment of all individuals in monitoring arm

- Participants diagnosed with invasive anal cancer
  - Treatment Arm: 9
  - Active Monitoring Arm: 21

- Cumulative progression to cancer at 48 months:
  - Treatment arm- 0.9%
  - Monitoring arm- 1.8%

- Median follow-up of 25.8 months, 57% reduction in anal cancer, NNT 111 (95% CI 6% to 80%, chi-squared = 4.74, P=.029)

MORE RESULTS

- Cancer incidence:
  - Treatment Arm: 173/100,000 person years of follow-up
  - Active Monitoring Arm: 402/100,000 person years

- Cancer risk:
  - Lesions ≤50% of the anal/perianal canal- 185/100,000 PY (95% CI: 115-298)
  - Lesions >50% of the anal/perianal canal- 1,047/100,000 PY (95% CI: 608-1803) (hazard ratio 5.26, 95% CI: 2.54-10.87)

Higher Cancer Incidence Than Expected

Cancer incidence in the treatment arm was 173/100,000 PY of follow-up, compared with 402/100,000 PY in the AM arm

- 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

the ANCHOR study

Implications of the ANCHOR study findings

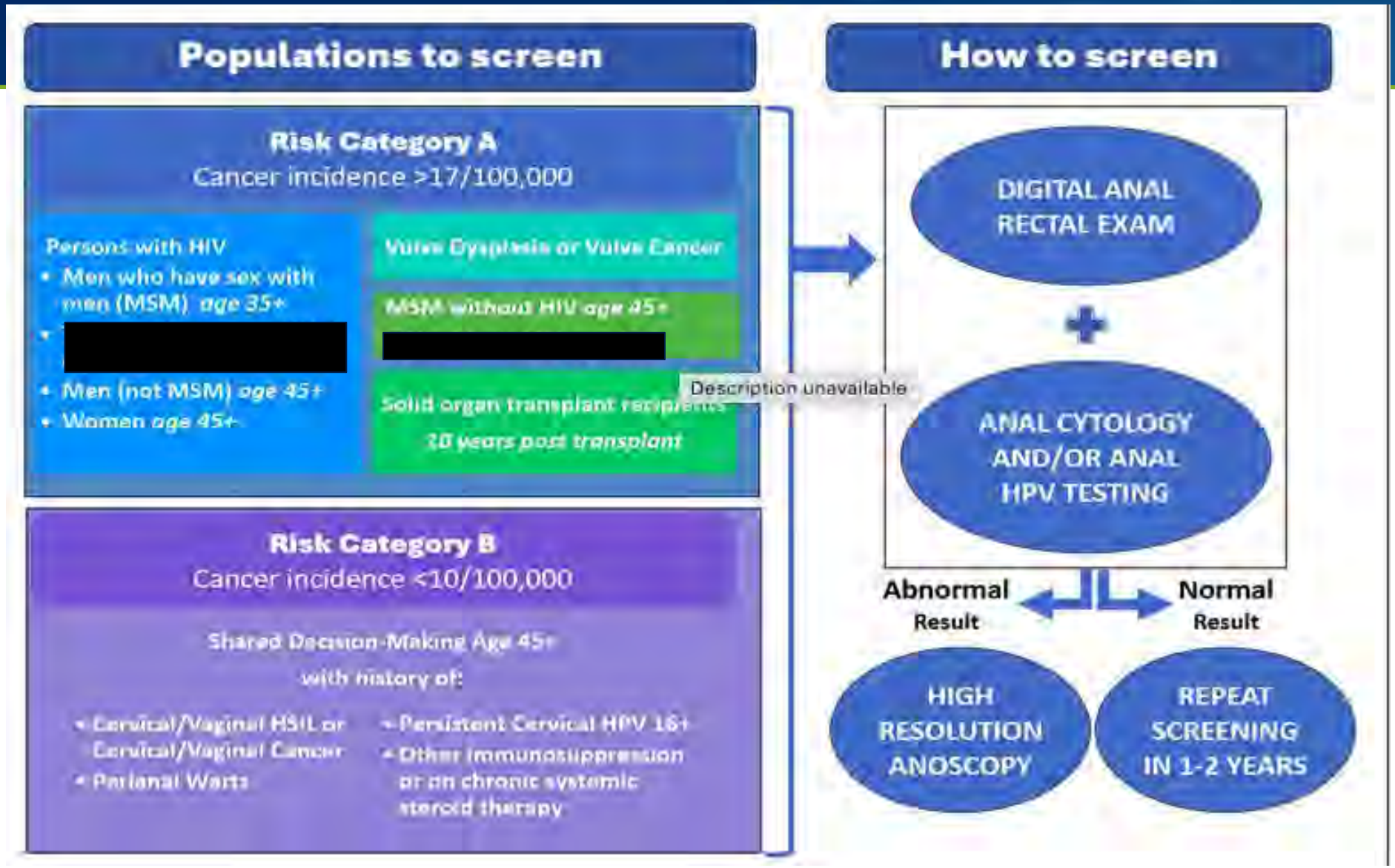
- Rate of progression from anal HSIL to cancer is high
- Treatment of anal HSIL is effective in reducing the incidence of anal cancer
- Extrapolation of results to other immunosuppressed groups at high risk of anal cancer
- This data supports the need for anal cancer screening and screening guidelines for all patients at high risk

Screening Guidelines

- International Anal Neoplasia Society
- NIH/CDC/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV
- Madison Clinic at Harborview Medical Center

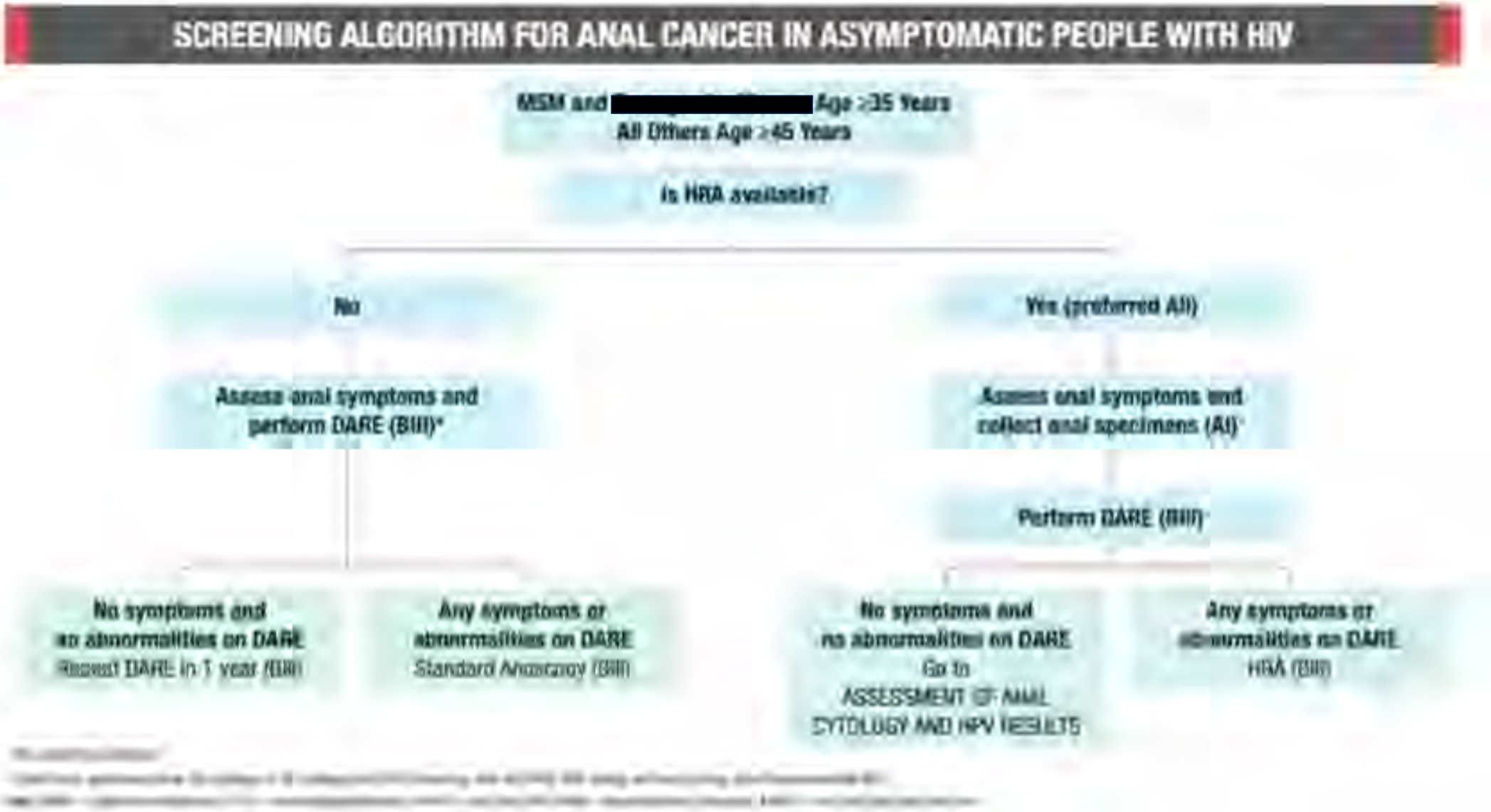
U.S. Department of Health and Human Services Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association, and Infectious Diseases Society of America; 2024 Jul 9.

International Anal Neoplasia Society (IANS)- January 2024



Stier EA, Clarke MA, Deshmukh AA, et al. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. *Int J Cancer*. 2024; 154(10): 1694-1702. doi:10.1002/ijc.34850

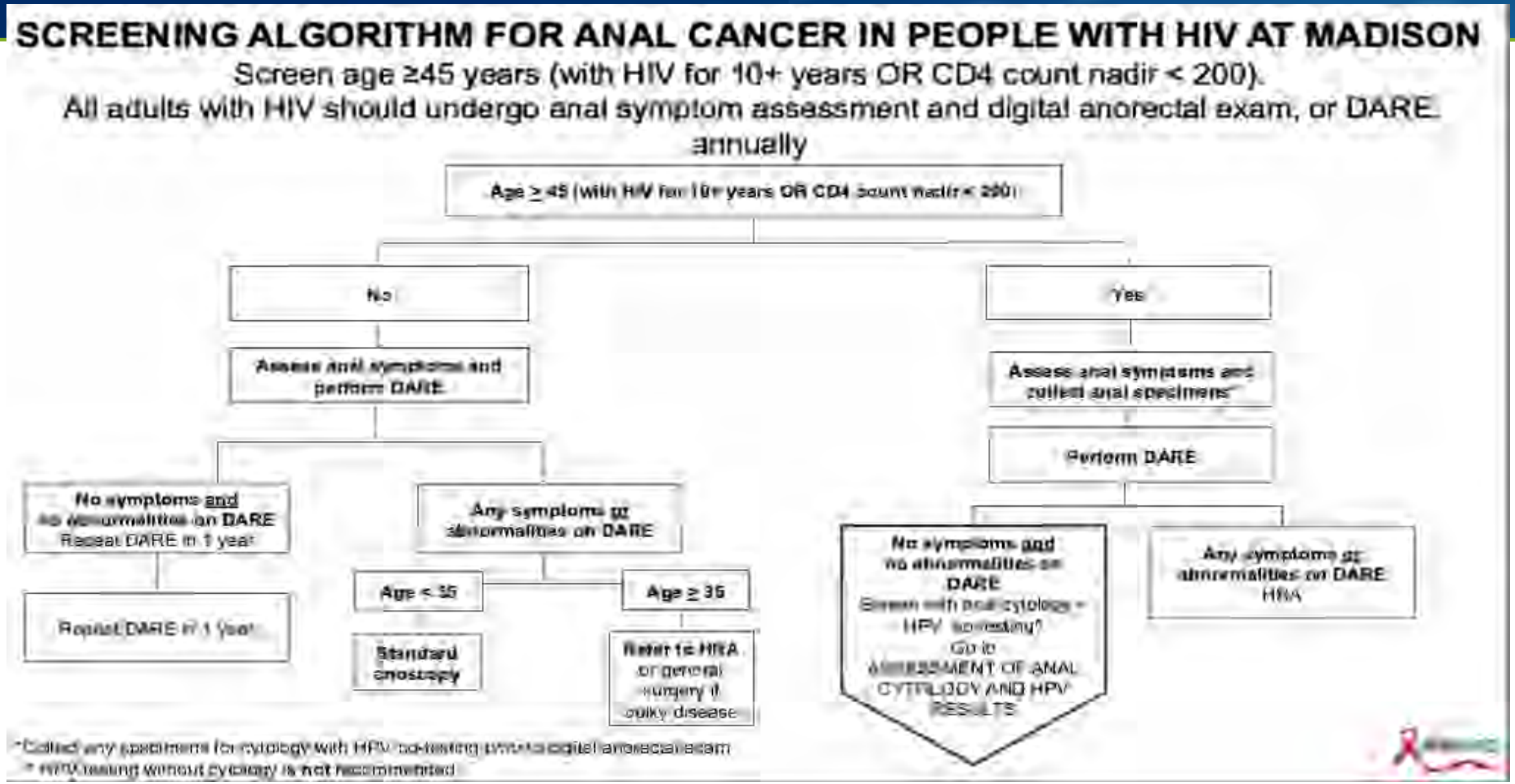
Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV - NIH/CDC/IDSA



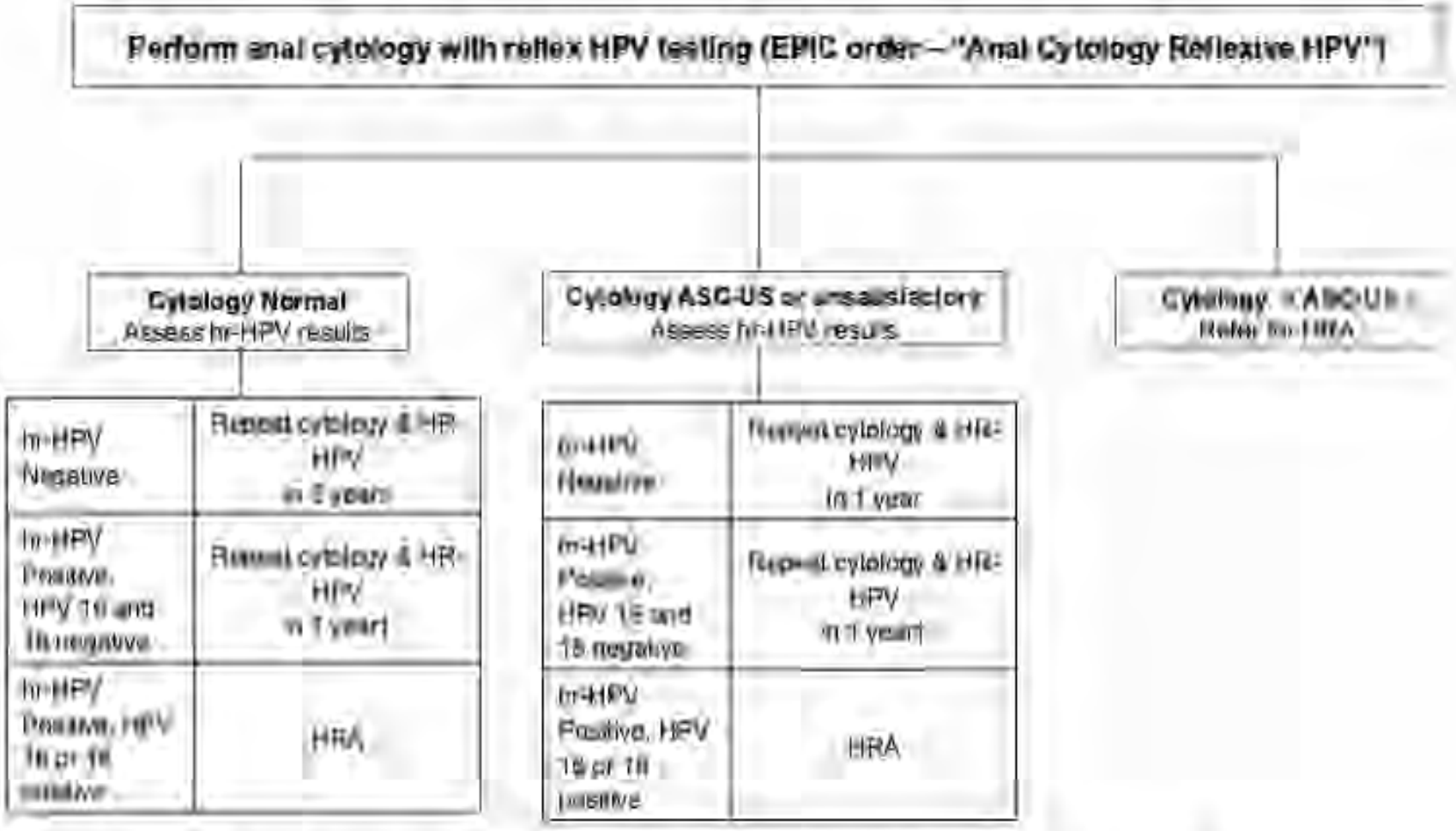
	NIH OAR Adult and Adolescent OI Guidelines	IAS Guidelines
Primary anal HPV testing alone without cytology as screening option	No	No
High-priority patients if HRA availability limited (no priority order specified in either guideline)	• Higher grade of cytologic abnormality • HPV16 on HPV testing • Smokers • >50 years of age • Longer known duration of HIV • History of AIDS	• Higher grade of cytologic abnormality • HPV16 on HPV testing

From Dr. Shireesha Dhanireddy's presentation, "Anal Cancer Screening" HIV ECHO 8.29.24

Madison Clinic Guidelines



ASSESSMENT OF ANAL CYTOLOGY AND HPV RESULTS IN PEOPLE WITH HIV



[1] If at repeat testing either cytology is ≥ ASCUS or any HR-HPV is detected, refer to HRA (BIII)

How to Perform an Anal Cytology (Pap Smear)

Gently spread the buttocks

Insert tap water-moistened Dacron swab until it bypasses the internal sphincter and abuts the distal wall of the rectum

Anal Cytology

Sweep in a circular fashion as the swab is withdrawn in order to sample cells from all aspects of anal canal.

Count to 10 while withdrawing the swab, sweeping the sides of the anal canal.

Vigorously shake in the Thinprep solution for 20-30 seconds.

Discard the swab.

Order non-Gyn cytology and select anal swab.

Slide modified from ASCCP HRA Course

Digital Anal Rectal Examination

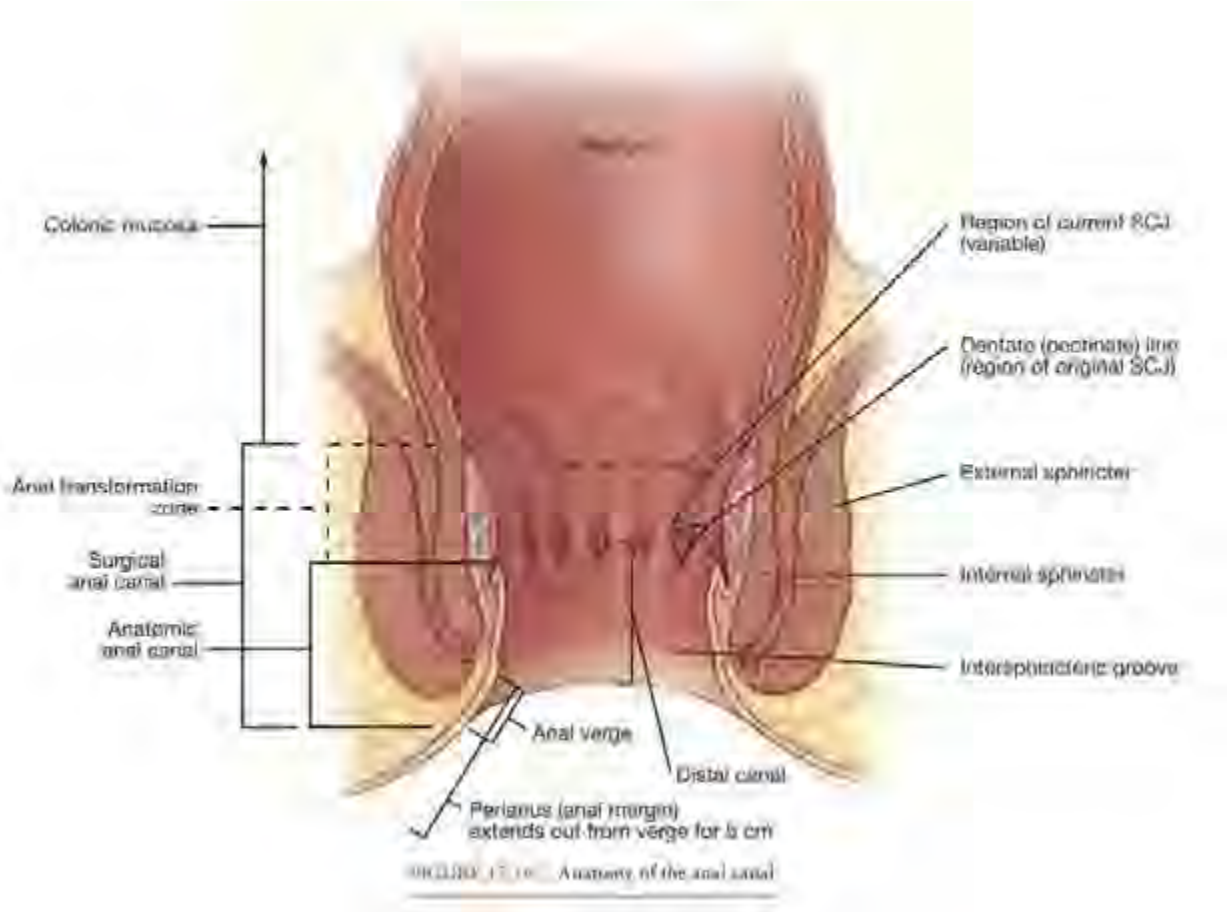
-Extension of digital rectal exam

-Palpation of 360 degrees of the walls of the anal canal

-Visualization/palpation of the anal margin, defined as 5 cm distal to anal verge

-Palpation of the perianus, prostate, rectovaginal septum

-You can sometimes feel something that you can't see



Slide modified from ASCCP HRA Course

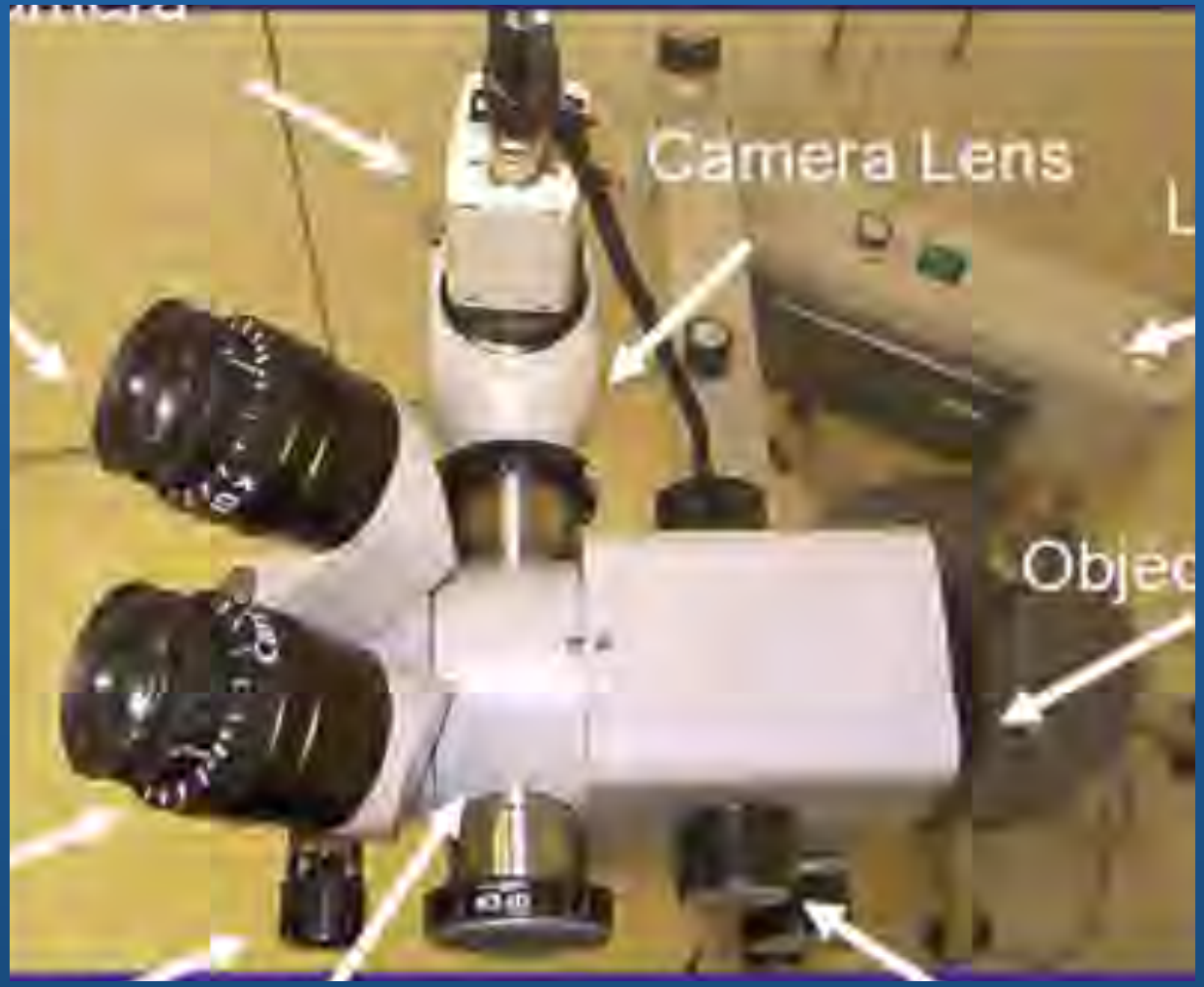
High-Resolution Anoscopy (HRA): Examination

- Thorough exam with biopsies, 15-20 minutes
- Areas to be examined:
  - Squamocolumnar Junction
  - Transition Zone
  - Anal Canal
  - Anal Verge
  - Perianal Skin

Satisfactory exam = ALL aspects viewed completely

Slide from ASCCP HRA Course

Anoscope with Image Capture



SCJ and the Transformation Zone

FIGURE 17.22. Rectal columnar epithelium and anal squamous epithelium abut at the SCJ. Note that the rectal mucosa is dark red compared to the lighter pink color of the anal epithelium. The AnTZ here is seen as a thin, white line of metaplasia.

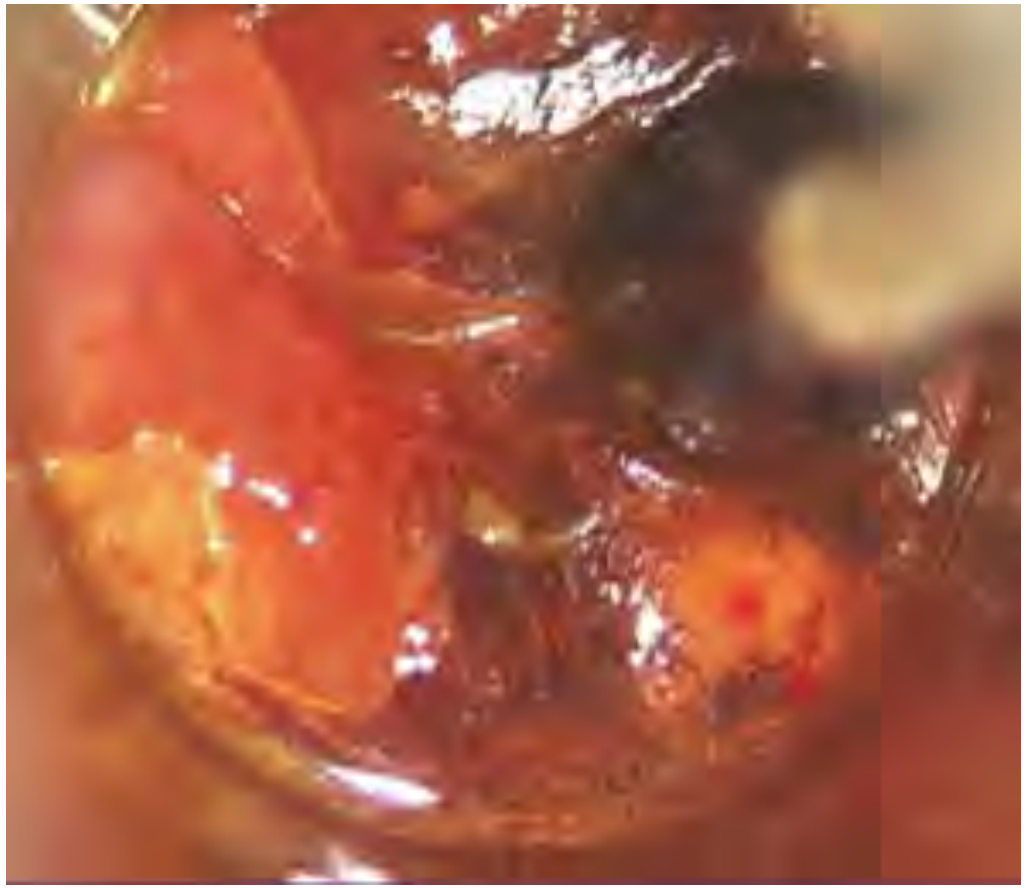
Squamocolumnar Junction (SCJ)

Slide from ASCCP HRA Course

Lugol's Solution

Lugol's solution applied after identifying all aspects of AnTZ with acetic acid

Normal tissue- dark brown



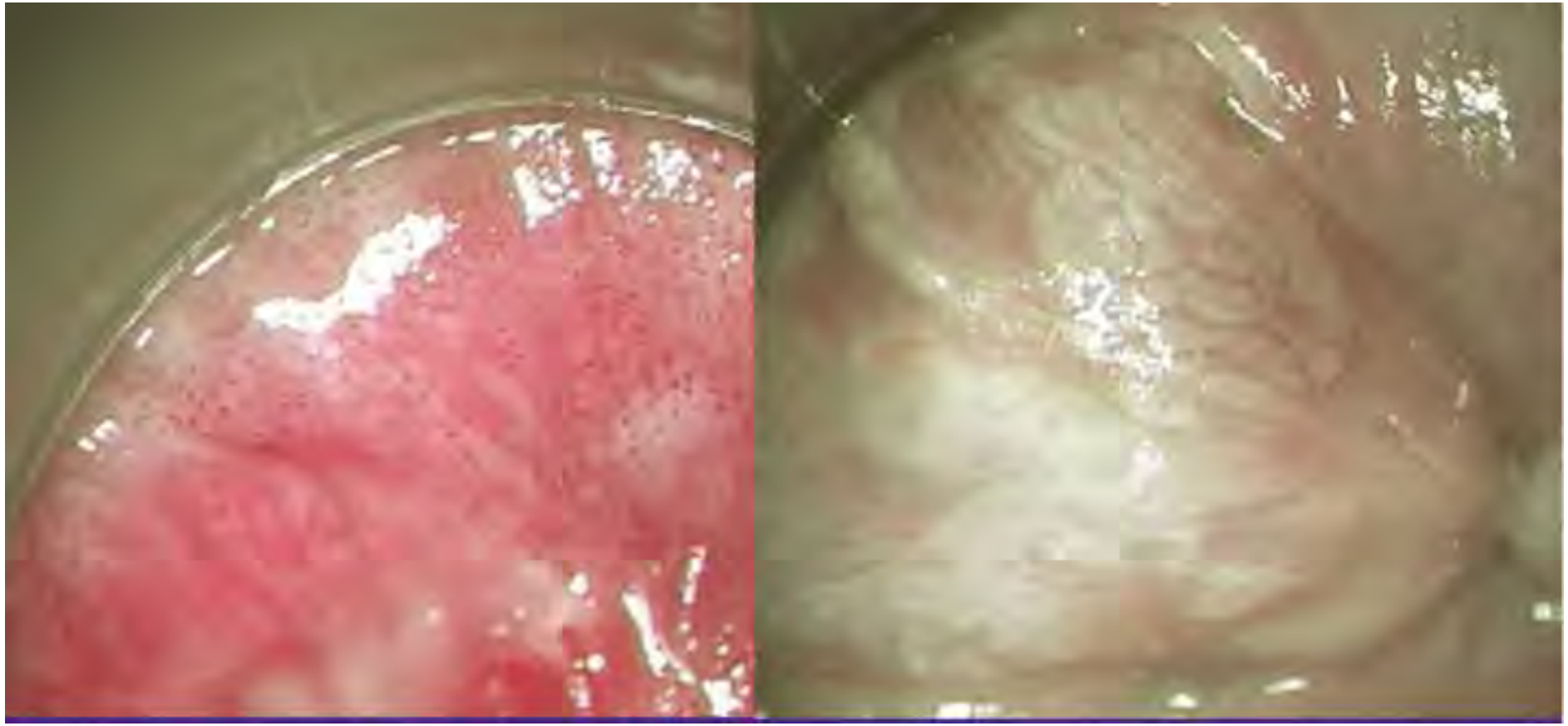
Slide from ASCCP HRA Course

HSIL (HGAIN) with striated vessels and “lacey metaplasia”

FIGURE 17.37. Striated vessels; biopsy showed HGAIN.

FIGURE 17.44. Atypical metaplasia with ringed glands; biopsy (*designated by circle*) showed HGAIN.

HSIL Vessels



Punctation

Mosaic Pattern

Slide from ASCCP HRA Course

Invasive anal SCCa

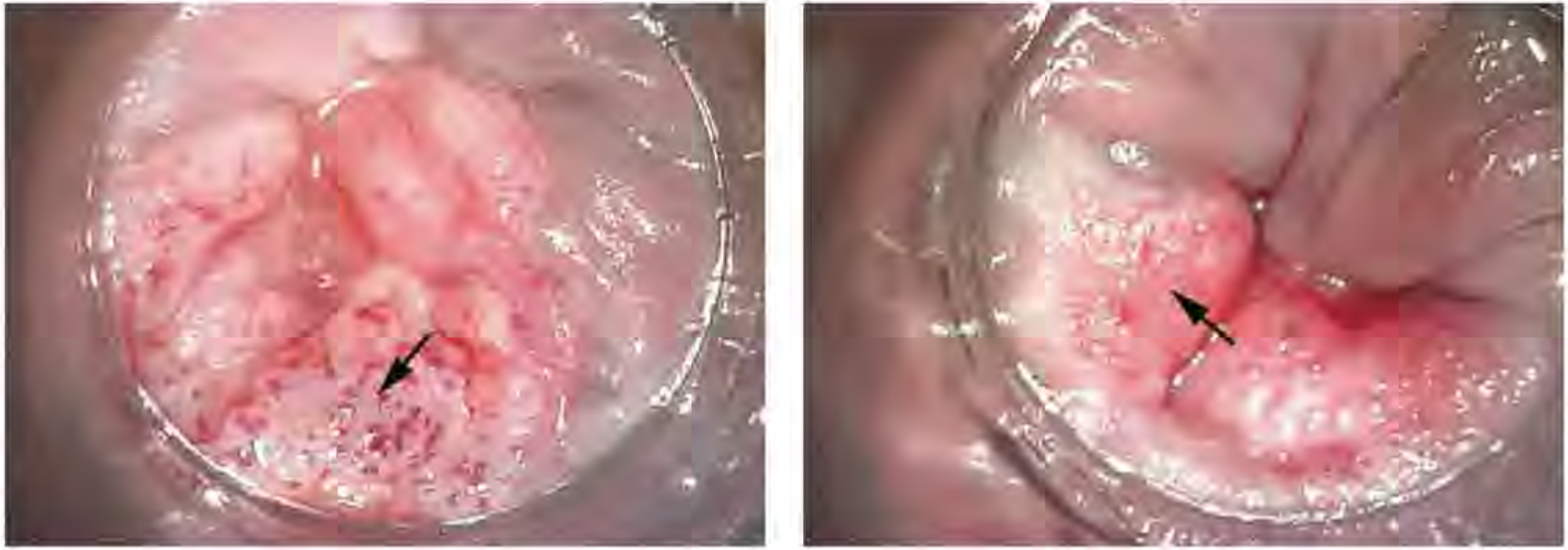


FIGURE 17.70. Patient had palpable thickening on DARE. HRA showed the mass with atypical vessels consistent with cancer. **A:** At SCJ. **B:** In distal canal, at *dentate line*. *Arrows* indicate biopsy sites performed in the office; biopsies showed invasive SCC.

Perianal HSIL

FIGURE 17.90. Perianal HGAIN: acetowhite, flat, granular, and thickened.

FIGURE 17.93. Perianal HGAIN: extensive lesion with flat and slightly raised areas at the base and center, and a raised thickened area with defined margins at the superior aspect of the lesion.

Invasive perianal SCCa- pre and post-CMT

Treatment with infrared coagulation or hyfrecation

https://www.zinnantisurgical.com/hra

Topical Treatments for HSIL and Condylomas

- **Imiquimod (Aldara)- TIW at night up to 16 weeks**
- **5-Fluorouracil (Efudex)- 5 days BID then 9 days off, 8 cycles**
- Trichloroacetic acid
- Podophyllotoxin- only used for perianal condylomas
- Sinecatechins (Veregan)
- Interferon
- Cidofovir (compounded)
- Cryotherapy (perianal only)

Some of these are not FDA-approved for treatment of condylomas. None are approved for the treatment of HSIL or intra-anal application.

Topically applied treatments for external genital warts in nonimmunocompromised patients: a systematic review and network meta-analysis. Br J Dermatol. 2019 Nov 1. doi: 10.1111/bjd.18638

ACIP HPV Vaccine Recommendations

- Children and adults aged 9 through 26 years
  - Routinely started at age 11-12
- Age 26- Everyone not adequately vaccinated
- Ages 27-45- Some adults if not fully vaccinated, shared decision making
- Not licensed for people older than 45

and me!

Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2019;68:698–702. DOI: http://dx.doi.org/10.15585/mmwr.mm6832a3

Ongoing Challenges and Future Goals

- Studies needed to evaluate screening guidelines
  - Effect on anal cancer incidence and mortality
- Optimization of screening algorithms
  - HR-HPV co-testing (not yet FDA approved)
  - Biomarkers for HSIL progression or regression
- HRA Availability
  - Training programs
  - Space and equipment

And More…

- Care Coordination
  - Cytologists/pathologists
  - Surgical teams for evaluation or treatment

- Patient Centered Care Improvement in HSIL treatment
  - Improvement in HSIL Treatment
  - Trauma Informed Care
  - Educational materials
  - Welcoming exam space

In Summary…

- Anal cancer incidence is high in people living with HIV
- HPV infection leads to HSIL; HSIL is a precursor to anal cancer
- High progression rate of HSIL to anal cancer in people living with HIV
- **ANCHOR study showed us that we can reduce the incidence of anal cancer in people living with HIV by treating HSIL**
- First anal cancer screening guidelines– IANS or NIH/CDC/IDSA to help determine who to screen, should tailor to HRA availability
- Vaccination against HPV helps prevent anal dysplasia in those not yet exposed
- More research to refine screening guidelines and treatment options
- More HRA providers needed!

Questions?

Thank You!