Outpatient Anal Cancer Screening
In the Era of COVID-19

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Professor of Medicine
University of California, San Francisco

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Disclosures

- Merck and Co- research and travel support
- Vir Biotechnologies- consultant, stock options
- Virion Therapeutics- stock options
- Vaccitech- consultant
Objectives

- Describe the epidemiology of anal HPV infection, high-grade squamous intraepithelial lesions (HSIL) and cancer among people living with HIV (PLWH)
- Describe recent advances in screening for anal cancer and HSIL
- Describe the progress of the ANCHOR Study
- Describe the impact of screening for and treating HSIL in the setting of the COVID pandemic
Age-Adjusted Incidence of Invasive Anal Cancer by Gender and Year of Diagnosis: United States

Anal Cancer Incidence Is Increasing In Women

SCCA among White women

Deshmukh AA, et al. 17th International Conference on Malignancies in HIV/AIDS

Incidence/100,000 (85% CI)

- **HIV-infected**
  - MSM 131 (109-157)
  - MSW 46 (25-77)
  - Women 30 (17-50)

Silverberg M et al. CID 2012; 54:1026-34
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
The future of HPV-related cancer in HIV-infected men and women

<table>
<thead>
<tr>
<th></th>
<th>Increased incidence of cancer</th>
<th>Decreased incidence of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>Possibly</td>
<td></td>
</tr>
<tr>
<td>Accelerated biological aging</td>
<td>Possibly</td>
<td></td>
</tr>
<tr>
<td>Lower nadir CD4 level</td>
<td>Likely</td>
<td></td>
</tr>
<tr>
<td>Lower current CD4 level</td>
<td>Possibly</td>
<td></td>
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<tr>
<td>Time on effective ART</td>
<td></td>
<td>Possibly</td>
</tr>
<tr>
<td>Earlier initiation of ART</td>
<td></td>
<td>Possibly</td>
</tr>
<tr>
<td>Screening for and removal of HSIL</td>
<td></td>
<td>Definitely (cervical)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possibly (anal)</td>
</tr>
<tr>
<td>HPV vaccination</td>
<td></td>
<td>Likely (in the future)</td>
</tr>
</tbody>
</table>
Overall HPV prevalence by sex, anal diagnosis and HIV status

Prevalence of HPV16, HPV18, and HPV31/33/45/52/58 by anal diagnosis and HIV status, in HPV-positive men and women

Future indicators: prevalence of AIN among MSM
Population-based data

AMC-072
HPV vaccination among HIV+ MSM 18-26 years

- 34% had HSIL at screening
- 93% had at least one anal HPV type
- 23/47/47/63% of participants were naïve at baseline to HPV 6/11/16/18, respectively

J. Palefsky, personal communication
High prevalence of anal HSIL in HIV+ women

- AMC-084- 27% of HIV+ women

Anal cytology screening for ASIL

Screen

- Normal
- ASCUS
- LSIL
- HSIL

- Repeat in 12 months (HIV+)
- Repeat in 2-3 years (HIV-)

High resolution anoscopy with biopsy

- No lesion seen
- LSIL
- HSIL

- Treat or follow
- Treat

High resolution anoscopy (HRA)

HRA is an *office-based* procedure examining the anus, anal canal and perianus using a colposcope or operating microscope with 5% acetic acid and Lugol’s solution.
Who should be screened?

- All HIV-positive men regardless of sexual orientation
- All HIV-negative MSM
- Women with high-grade cervical or vulvar lesions or cancer
- All HIV+ women
- All men and women with perianal condyloma
- Solid organ transplant recipients
  - Over 25 years if immunosuppressed, inc. HIV
  - Over 40 years if immunocompetent
Digital anorectal exam (DARE!)
Challenges of anal cancer screening

- Limited sensitivity of anal cytology
- Undercalls severity of lesions
## Cytology testing to screen for anal HSIL

<table>
<thead>
<tr>
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<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Absolute risk (%)</th>
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<tbody>
<tr>
<td>ASC-US</td>
<td>37/308 (12.0, 8.8 to 16.1)</td>
<td>400/634 (63.1, 59.3 to 66.8)</td>
<td>12/241 (5.0, 2.9 to 8.5)</td>
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<tr>
<td>LSIL</td>
<td>49/308 (15.9, 12.2 to 20.4)</td>
<td>463/634 (73.0, 69.4 to 76.3)</td>
<td>37/271 (13.7, 10.1 to 18.3)</td>
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<tr>
<td>ASC-H</td>
<td>66/308 (21.4, 17.2 to 26.3)</td>
<td>634/634 (100.0, 99.4 to 100.0)</td>
<td>49/220 (22.3, 17.3 to 28.2)</td>
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<td>HSIL</td>
<td>143/308 (46.4, 40.9 to 52.0)</td>
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<tr>
<td>SCCA</td>
<td>1/308 (0.3, 0.1 to 1.8)</td>
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Sensitivity, specificity and positive predictive value for detection of anal HSIL

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<td>231/309 (74.8, 69.6 to 79.3)</td>
<td>440/634 (69.4, 65.7 to 72.9)</td>
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<td>39/73 (53.4, 42.1 to 64.4)</td>
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HPV testing for anal screening

• “Basket” tests have good sensitivity but low specificity
• Specific types such as HPV 16 have low sensitivity but high specificity

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HPV testing for anal screening

<table>
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<tr>
<th>Cytology</th>
<th>HPV result comparison</th>
<th>Absolute risks (%)</th>
<th>Relative risk (95% CI)</th>
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<tr>
<td>Normal</td>
<td>Aptima+ vs. Aptima-</td>
<td>16.7 vs. 1.6</td>
<td>10.4 (2.9 to 37.0)</td>
</tr>
<tr>
<td>ASC-US</td>
<td>Aptima+ vs. Aptima-</td>
<td>26.2 vs. 8.0</td>
<td>3.3 (1.8 to 6.0)</td>
</tr>
<tr>
<td>LSIL</td>
<td>Aptima+ vs. Aptima-</td>
<td>30.4 vs. 11.6</td>
<td>2.6 (1.4 to 4.9)</td>
</tr>
<tr>
<td>Normal</td>
<td>Aptima 16+ vs. Aptima 16-</td>
<td>40.0 vs. 4.2</td>
<td>9.4 (2.8 to 32.4)</td>
</tr>
<tr>
<td>ASC-US</td>
<td>Aptima 16+ vs. Aptima 16-</td>
<td>35.3 vs. 12.2</td>
<td>2.9 (1.4 to 6.0)</td>
</tr>
<tr>
<td>LSIL</td>
<td>Aptima 16+ vs. Aptima 16-</td>
<td>44.7 vs. 17.6</td>
<td>2.5 (1.6 to 4.1)</td>
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J. Palefsky, personal communication
### Sensitivity, specificity and positive predictive value for detection of anal HSIL

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<td>Screening combo</td>
<td>235/309 (76.1, 71.0 to 80.5)</td>
<td>599/634 (94.5, 92.4 to 96.0)</td>
<td>235/270 (87.0, 82.5 to 90.5)</td>
</tr>
</tbody>
</table>

Screening combo: (Normal cytology and HPV 16+) or (ASC-US and HPV 16+) or (LSIL and HPV 16+) or (cytology > LSIL)

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Cytology and HPV testing for screening

- HSIL/ASC-H on cytology → refer
- Anything other than HSIL → test for HPV 16
- HPV 16+ → refer
- HPV 16- → repeat
  - Normal- repeat in 2-3 years?
  - ASC-US-repeat in 1 year?
  - LSIL- repeat in 6 months?
Other approaches

- Methylation
- P16/INK4A
Screening for anal cancer

Yes or no?

IDSA
Oct 5, 2019

Joel Palefsky
Department of Medicine
University of California, San Francisco
Does screening for anal cancer and its precursors meet current screening standards?

- Dobrow MJ et al. CMAJ 2018 April 9;190:E422-9.
  - Wilson and Jungner’s 10 principles of screening
• Incidence of anal cancer is high in well-defined at-risk populations
• Treatment of cervical HSIL is proven to reduce the incidence of cervical cancer
• Treating anal HSIL will therefore reduce the incidence of anal cancer and so we should be screening for anal HSIL
Here’s why not not

• Anal and cervical HSIL are very similar - treatment should work: Here’s why not:
  • 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!
"I just want to apologize beforehand if you miss."
Aim 1: To determine whether treating anal high-grade squamous intraepithelial lesions (HSIL) is effective in reducing the incidence of anal cancer in HIV-infected men and women
ANCHOR study

- **Aim 2**: To determine the safety of infrared coagulation (IRC), electrocautery, imiquimod, laser and 5-fluorouracil treatments 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))

NCI UM1CA121947 and OAR
• **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;
  - Identify medical history and behavioral risk factors for HSIL progression to cancer

NCI UM1CA121947 and OAR
Screen >17,385

Enroll 5,058

Retain for 5 or more years

HIV+ Men and Women over 35
Screened for HSIL

HSIL Found
- Enrolled and Randomized
- Every 6 Months:
  - Digital Rectal Exam
  - Anoscopy
  - Biopsy (if needed)
  - Anal Swab
  - Blood Sample
  - Cancer Not Found
  - Cancer Found
- Exit Study
  - Referred for Evaluation and/or Treatment

HSIL Not Found
- Not Enrolled
- Every 6 Months:
  - Digital Rectal Exam
  - Anoscopy
  - Biopsy (if needed)
  - Anal Swab
  - Blood Sample
  - HSIL Removed
  - Cancer Not Found
  - Cancer Found
- Exit Study
  - Referred for Evaluation and/or Treatment
ANCHOR study as of 8/28/20

• Screened: 9684
• Enrolled: 3924

• Call 415-353-7443
• www.anchorstudy.org
Until ANCHOR results are available:

- Refer eligible patients to ANCHOR
- For patients ineligible or not interested in ANCHOR: screen with cytology or HPV and refer for HRA
Screening for and treating HSIL in the COVID era
In Memory

Barbara Winkler, MD
IANS Guidelines for the practice of HRA in the era of COVID-19

April 8, 2020

Key Points

- COVID-19 responses are rapidly changing and vary considerably with local epidemiology and resources. You can find out about what is happening in other places [here](https://www.iansoc.org).
- If resources allow, prioritize patients at highest risk of anal cancer risk – many/most will be able to be deferred for at least three months.
- Assess all patients for COVID-19 risk at time of booking and on day of procedure. HRA only indicated for those with highest risk of anal cancer and low risk of having COVID-19. Consider delaying HRA, even in these individuals, if they fall into any of the highly vulnerable COVID risk groups.
- If HRA is still indicated, then follow local Infection Control guidelines as a minimum.
Do we really need guidelines for HRA during COVID-19 pandemic?

“Consequent to COVID-19 pandemic, all International and National Societies published countless guidelines about the management of patients affected by COVID-19. In spite of this IANS proposed its guidelines for the use of HRA in anal cancer and its precursors. Considering the costs to deal with COVID-19, the deficiency of healthcare professionals and the lack of worldwide evidence consensus on HRA, this examination cannot be considered mandatory during the COVID-19 pandemic. DARE with biopsy of suspicious palpable lesions in symptomatic patients could be considered enough during this period. Probably a latency of 6-12 months is reasonable for these patients without affecting the natural history of AIN.”

Mistrangelo M et al. Colorectal Dis. 2020
“Many organisations have issued guidelines regarding the management of cancer in the era of COVID-19. In England at least, a new diagnosis of anal cancer would clearly be allocated a “Priority level 1”, as there is a curative therapy with a high (>50%) chance of successful treatment. Newly diagnosed anal cancers clearly have better outcomes when diagnosed earlier, with increasing evidence that chemoradiotherapy may be avoided in small cancers such as superficially invasive squamous cell cancers”

Hillman R. et al. Colorectal Dis. 2020
<table>
<thead>
<tr>
<th>Risk assessment</th>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>Priority</td>
<td>Urgent</td>
<td>As soon as possible</td>
<td>May be deferred</td>
</tr>
<tr>
<td>Definition</td>
<td>HRA should occur within one month, unless epidemic situation is extreme - in which case, prioritise biopsy of clinically invasive lesions. Prioritized as first to be scheduled.</td>
<td>HRA performed within 6 months, if possible. Symptom check-in by phone or telemedicine, repeat at 3 months.</td>
<td>Defer HRA until resumption of normal clinic scheduling. Symptom check-in by phone or telemedicine, repeat at 3-6 months.</td>
</tr>
<tr>
<td>Principal objective</td>
<td>Clinically highly suspicious of cancer. Digital Anal Rectal Examinations are an integral part of such an assessment.</td>
<td>Within 6 months of first cancer treatment and those treated within 2 years ago.</td>
<td>Low risk of cancer (unlikely within one year).</td>
</tr>
<tr>
<td>Clinical cancer assessment</td>
<td>HSIL clinically suspicious for cancer. Cytology or histology suspicious, but not diagnostic of cancer.</td>
<td>Features concerning for progressive disease in previous exam (e.g. lesion characteristics that are very prominent). Cytology HSIL, not yet assessed with HRA.</td>
<td>No current evidence of HSIL. No concerning features in previous exam. Cytology &lt;HSIL or ASC-H (PHSIL).</td>
</tr>
<tr>
<td>HSIL surveillance</td>
<td>Symptoms or signs that have worsened or recurred</td>
<td>Symptoms present but unchanged in 6 months &gt; 1 year since last exam.</td>
<td>No symptoms/signs.</td>
</tr>
<tr>
<td>Investigation of symptoms/signs (lump, bleeding, pain, tenesmus)</td>
<td></td>
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</table>
Fecal shedding of SARS-CoV-2

- 28 of 42 (67%) patients with NP shedding tested positive for SARS-CoV-2 RNA in stool specimens,
- not associated with gastrointestinal symptoms
- 18 of 28 (64%) remained positive for viral RNA in the feces after the pharyngeal swabs turned negative.
- duration of viral shedding from the feces after negative conversion in pharyngeal swabs was 6-10 days, regardless of COVID-9 severity

IANS guidelines
Summary recommendations

• Consider seeing only patients assessed to be at very high risk of anal cancer. DARE may provide a simple and relatively safe means of assessing risk.
• Aerosol-generating procedures such as laser or electrocautery are rarely necessary in an urgent situation. They should only be undertaken with full PPE including FFP3/N95 masks.

www.iansoc.org
Screening in the COVID era

- Ongoing assessment of risk:benefit ratio
- Can defer screening of asymptomatic individuals with a negative DARE
- Consider referring symptomatic individuals
- Refer those with a mass on DARE
Summary

- Anal cancer is increasing in general population, remains high in HIV+ population
  - In the long run we can eliminate anal cancer

- The HPV vaccine is highly efficacious and is an important tool to prevent anal cancer
  - Vaccinate age 26 and under!
  - After age 26 = individual decision
Thank You for Your Attendance!
Please visit us at:

www.prn.org