Minding the Behind: Anal Cancer Epidemiology and Screening

September 14, 2021
Disclaimer

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- Ask a question in chat at any time
  - Click on the speech bubble icon in the lower right corner to open chat

- Use the ‘raise hand’ feature if you wish to ask a question verbally
  - Click on the Reactions (face) icon, then click on Raise Hand.
  - When we call on you, unmute and turn on your video to ask your question

- Polling
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Minding the Behind: Anal Cancer Epidemiology and Screening

September 14th, 2021
Objectives

- Utilize the natural history of anal HPV infection to understand the rationale for screening and prevention of anal cancer
- Summarize current epidemiology of anal cancer risk in different high-risk populations and the sensitivity and specificity of cytology and HPV testing to detect high-grade lesions of the anal canal
- Outline limitations and evidence gaps in current recommendations for anal cancer screening
- Describe how to properly complete a digital anorectal exam and anal PAP smear
- Identify when it is appropriate to refer for subspecialist management
Case #1 – Mr. S

25 y/o cisgender male (he/him/his)

• HIV positive since 19 y/o (2015)
• MSM
• Labs: Last CD4 782, Viral load < 20 – 11/2020
  • CD4 nadir: 340 (2015)
  • Peak Viral load 560,000 (2015), virally suppressed since early 2016
• Multiple unprotected partners, multiple STIs – early latent syphilis 2019, rectal and throat GC 2015, rectal chlamydia x1 2018.
  • Screened at each HIV follow-up visit
Poll Question #1

Which HIV positive patient is at highest risk for anal cancer?

1. HIV + MSM who is 20 years old and has multiple sexual partners
2. HIV + MSM who is 65 years old and is in a monogamous relationship, lowest CD4 count was 452
3. HIV + MSM who is 65 years old and is in a monogamous relationship, lowest CD4 count was 53
4. HIV + heterosexual male who is 65 years old and in a monogamous relationship
Anal cancer risk scale

Clifford et al., IJC 2020, 148(1):38-47
Biomarkers: CD4 nadir and prolonged CD4 immunosuppression

In a study combining 21 North American cohorts of PLWH, severe (nadir) and prolonged HIV-induced immunosuppression were the best predictors for anal cancer risk.

- Overall CD4 nadir, HR for <50 vs ≥500 cells/μL, 13.4 (95% CI 3.5-51.0)
- Prolonged CD4 <200 cells/μL from 8.5 to 4.5 years in the past, HR for 100% of the time period vs. 0%, 3.1 (95% CI 1.5-6.6)

North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)
- 21 cohorts of PLWH ≥18years (n=102,777; Anal cancers=492)

Poll Question #2

Would you screen Mr. S for anal cancer (25 y/o M, well-controlled HIV, multiple partners/STIs)?

1. Yes
2. No
3. I don’t know
Poll Question #3

If you would screen Mr. S, how would you screen?

1. Digital Anorectal Exam (DARE)
2. DARE + Anal PAP + HPV
3. DARE + Anal PAP
4. Anal PAP only
US Preventive Services Task Force recommendations for anal cancer screening do not exist

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

– Specialists recommend
  • DARE (moderate recommendation), anal cytology, high-resolution anoscopy (optional recommendation)
  • Make sure follow-up is available regardless of screening type

2021 CDC STI Treatment Guidelines

– DARE should be performed in 1) persons with HIV and 2) MSM without HIV who have a history of receptive anal sex
Natural history of anal HPV infection

Adapted from Schiffman & Wentzensen, 2010

- Uninfected anal canal
- HPV-infected anal canal and persistence
- Precancer (lesions)
- Cancer

Screen here for anal precancers? (a cervical cancer screening model)
And/or screen here for early anal cancer? (DARE)
Obtaining Anal Swabs – Cytology or HPV

• Water-moistened synthetic swab – Dacron
• Blind method is preferred and provides consistently high-quality samples.
• No Lubricant - interferes with the sample
• Insert swab ~ 5 cm/point of resistance
• Slowly remove, firm circular motion
• Count to 10 or more slowly removing
• Sample the verge
• Transfer sample to liquid-cytology vial vigorously swirling

Darragh, T & Winkler, B. Sexual Health 2012;9: 556-561
Digital Anorectal Examination

• Lubricated finger
• Slow deep breaths
• Steady pressure; May ask to bear down
• Insert gently until the “open space” of the rectum
• Gently feel the circumference at every level
• Slowly and firmly ~ 1 minute to complete
• Repeat if unsure
• Note blood or discharge

Hillman, R.J. et al. J Low Genit Tract Dis 2019;23: 138-146
Case #1 – Mr. S

Anal Cancer Screening History:

• Q 2 years since diagnosis – NIL
• 1/2021
  • ASCUS, + HPV (other (non 16,18) high-risk genotype)
  • Digital Anorectal Exam: No lesions identified
Poll Question #4

What would you do next for Mr. S?

1. Send to colorectal specialist for High-Resolution Anoscopy
2. Repeat HPV, Anal Pap, and DARE in 6 months
3. Repeat HPV, Anal PAP, and DARE in 1 year
4. Nothing, he is too young to screen
Poll Question #5

Mr. S is worried about the results and very nervous that he has cancer, what would you say to him about his risk of anal cancer?

1. Most patients with positive cytology (anal PAP) DO NOT have pre-cancerous or cancerous lesions of the anorectum

2. Most patients with positive high-risk HPV DO NOT have pre-cancerous or cancerous lesions of the anorectum

3. If you were negative for high-risk HPV, I could say with fair confidence that you DO NOT have any precancerous or cancerous lesions

4. All of the above
Biomarkers: HPV genotypes and contribution to anal cancer

Lin et al., Lancet Infect Dis 2017, 123(23): 4530-4534
Biomarkers: Pap cytology and hrHPV for hHSIL

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<tbody>
<tr>
<td></td>
<td>HIV+ MSM</td>
<td>HIV+ women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>363</td>
<td>1504</td>
<td>229</td>
<td>178</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91%</td>
<td>85%</td>
<td>83%</td>
<td>89%</td>
</tr>
<tr>
<td>Specificity</td>
<td>44%</td>
<td>33%</td>
<td>50%</td>
<td>36%</td>
</tr>
<tr>
<td>1-NPV</td>
<td>NR</td>
<td>25%</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
<td>96%</td>
<td>77%</td>
<td>96%</td>
</tr>
<tr>
<td>Specificity</td>
<td>29%</td>
<td>27%</td>
<td>67%</td>
<td>33%</td>
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<tr>
<td>1-NPV</td>
<td>NR</td>
<td>9%</td>
<td>11%</td>
<td>5%</td>
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</tbody>
</table>

Clarke, et al - among HIV+ MSM, hrHPV negativity indicates low risk for HSIL/AIN2+ for at least 2 years compared to negative cytology.

Gaisa et al. JID 2021, Clarke et al., CID 2018, Chiao et al., AIDS, 2020
Populations at increased risk for anal cancer

Anal cytology

Unsatisfactory, Benign, ASCUS

High-risk HPV testing

Positive

HRA

Negative

Repeat cytology in 1 year

LSIL, ASC-H, HSIL

HRA

Gaisa et al, JID 2021 (in press)
Key Points for Subspecialist: Case #1

- Age – 25
  - Low risk of anal cancer
- High Risk HPV +
  - expected in the age group
- Rectal STI/inflammation
- Bottom line – what would I do?
  - Repeat Cytology
  - Repeat DARE
  - Anoscopy
  - Discuss HRA with patient
  - Cytology in 6 months
High Resolution Anoscopy (HRA)

A procedure used to examine the anal canal and perianus. Chemical enhancement and colposcope are used with the goal of identifying precancerous lesions.

Image Source: Sarah Lundeen
Poll Question #6

Would HPV vaccination help Mr. S if he were vaccinated at this time?

1. Yes
2. No
3. We don’t know
## HPV vaccine efficacy for HIV+ adults

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine Group</th>
<th>Control Group</th>
<th>Efficacy (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent anal infection</td>
<td>n 286</td>
<td>n 283</td>
<td>21% (-61% -61%)</td>
</tr>
<tr>
<td>Improvement of anal hHSIL</td>
<td>n 288</td>
<td>n 286</td>
<td>0% (-44% -31%)</td>
</tr>
</tbody>
</table>

Wilkin et al., CID 2018, 67(9):1339-1346
Case #2 – Mr. M

54 y/o cisgender male (he/him/his)

- HIV positive since 2010 (thrush)
- MSM, in long term, monogamous relationship
- Labs:
  - 1/21: VL < 30; CD4 1078
  - CD4 nadir: 250, VL peak 950,000
- Other co-morbidities: Hypertension, CKD stage 3, chronic sinusitis
Case #2 – Mr. M

Anal history:

– Never screened
– 3/21 – partner noticed anterior rectal lump, no pain, no bleeding
– DARE: Anterior rectum, 1cm firm lump noted, not painful, moveable. 1cm deep. Not able to visualize.
– Cytology: ASCUS
– HPV: + other high-risk HR HPV
Discussion Question

What is your differential diagnosis for Mr. M?

- Please place answers in chat
Key Points for Subspecialist: Case #2

- Cytology and HPV would not change my initial investigation
- Repeat DARE and perform anoscopy or HRA
- Palpate inguinal nodes
- Get tissue diagnosis - If not an obviously “normal” finding
Possible findings: Normal finding? - unlikely in this case

Hypertrophic anal papillae  Thrombosed hemorrhoid in the canal

Fiber Supplement and bowel regimen if needed

Images Source: Sarah Lundeen
Condyloma (Wart) or Low Grade (LSIL)

Soft, fleshy, “frondy” pale/white

High Grade (HSIL)

Firm but not Fixed; abnormal vessels

Images Source: Sarah Lundeen
Possible findings: Cancerous lesion

Internal: Firm, Fixed, Friable
External: Firm, Fixed, ulcerated

Images Source: Sarah Lundeen
ANCHOR Study

Anal Cancer HSIL Outcomes Research

• National Institutes of Health (NIH)-funded study with the primary objective of determining whether treating anal HSIL is effective in reducing the incidence of anal cancer in people living with HIV.

• This study aims to understand if “anal cancer can be prevented by routine screening and removal of precancerous cells. This strategy has reduced cervical cancer rates by 80%” but is unclear if it prevents anal cancers as well.

https://anchorstudy.org/
Treatment for Anal Dysplasia

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Disease Factors</th>
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<tbody>
<tr>
<td>– Comfort &amp; Safety</td>
<td>– Immune Status</td>
</tr>
<tr>
<td>– Transportation</td>
<td>– Symptomatic</td>
</tr>
<tr>
<td>– Ability &amp; Willingness</td>
<td>– LSIL/HSIL/CA</td>
</tr>
<tr>
<td></td>
<td>– Extent/number/size</td>
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<tr>
<th>Patient-applied Therapy</th>
<th>Office-based Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Podofilox 5% - perianal</td>
<td>Trichloroacetic Acid (TCA) 80-90%</td>
</tr>
<tr>
<td>Imiquimod 5% or 3.75% - LSIL</td>
<td>– intra-anal and perianal</td>
</tr>
<tr>
<td>Sinecatechins 15% - LSIL/perianal</td>
<td>Cryotherapy - perianal</td>
</tr>
<tr>
<td>5-fluorouracil HSIL – off label</td>
<td>Ablation - anal canal anesthesia</td>
</tr>
</tbody>
</table>

Most FDA approved for LSIL/Warts. All off label for intra-anal

Infrared coagulation (IRC)

Hyfrecation
Cases #3 and #4 – missed opportunity?

Mr. W (he/him/his):
- 74 y/o heterosexual cisgender male, HIV +
- HIV: Dx 1990 in Africa, lowest CD4 200s, but maintained viral suppression, CD4 600s on EVG/COBI/TAF/FTC + DRV
- 2018: Rectal bleeding/mass → Diagnosed with metastatic anal cancer.
- 2020: passed away on hospice from cancer complications + COVID

Mrs. J (she/her/hers):
- 68 y/o heterosexual cisgender female, HIV –
- ESRD on dialysis since 2010. No history of solid organ transplant, severe vascular dementia, hypertension, CVA.
- Hx of CIN I on cervical Bx 2013, subsequent PAPs x2 negative.
- 2019: Rectal bleeding/mass → Anal cancer
- 2020: Passed away from complications of anal cancer on hospice
Poll Question #7

How should these difficult experiences change my practice (choose what you feel is the best answer)?

1. They shouldn’t: we still don’t know the risk level of these patients and if screening is indicated and helpful.

2. I should do DARE/PAP/HPV on the HIV + heterosexual males > 45 years old.

3. I should do DARE/PAP/HPV on solid organ transplant patients but not patients on dialysis.

4. I should do DARE/PAP/HPV on women with a history of vulvar or cervical pre-cancer or cancer.
Mean anal canal tumor size at presentation 3.6 cm in diameter

n = 1,622 Texas Cancer Registry, 2000-2010

- > 5 cm: 18%
- < 1 cm: 13%
- 1 - 1.99 cm: 20%
- 2 - 5 cm: 49%

66 French women and men with early invasive anal cancer (≤1 cm tumors): 5-year disease-specific survival was 100%

Ortholan et al., 2005

15 PLWH with T1N0M0 cancer of the anal verge (below the dentate line): 4-year disease-specific survival was 100%

Alfa-Wali et al., 2016
Anal cancer risk scale

**FIGURE 5** Anal cancer risk scale. 95% CIs around the point estimates can be found in the relevant Figures 1-4 and Tables S1 and S2. Estimates for HIV-negative men and men are shown, without labels, for age-groups <30, 30 to 44, 45 to 59, and ≥60 years (see Section 3). CI, confidence interval; MSM, men who have sex with men; MSW, men who have sex with women. yrs, years old; yst, years since transplant

Clifford et al., IJC 2020, 148(1):38-47
Prevent Anal Cancer Study in Milwaukee

Approach

Uninfected anal canal → infection → HPV-infected anal canal and persistence → progression → Precancer (lesions) → invasion → Cancer

Prevent Anal Cancer Study (PAC Study)

400 Milwaukee MSM and trans persons ≥ 25 years are randomized to two arms:
- 200 receive a self-swabbing kit at home
- 200 receive a clinician-swabbing at a clinic
PAC Self-Swab Study Aims

1) Determine compliance with annual anal HPV DNA specimen collection and high-resolution anoscopy.

2) Determine factors associated with annual screening compliance.

3) Assess the performance of two molecular markers: HPV DNA persistence and host/viral DNA methylation.
Relevant Resources & References

Screening for anal neopl...
Additional Resources

• AETC National Coordinating Resource Center (NCRC): aidsetc.org/
• National Clinician Consultation Center (NCCC): nccc.ucsf.edu/
• National HIV Curriculum (NHC): www.hiv.uw.edu/
• Midwest AETC: https://www.matec.info/calendar
Upcoming Events

St. Louis STI/HIV Prevention Training Center
A Review of the 2021 CDC STI Treatment Guidelines
Thursday, September 23, 2021 | 8:00AM - 12:00PM Central Time

Course Objectives

- Describe changes to STI management in the 2021 CDC STI Treatment Guidelines
- Detail new treatment recommendations for gonorrhea and chlamydia
- Discuss impact of STI Treatment Guidelines on partner services
Upcoming Events

MATEC-Illinois

24th Annual MATEP HIV Treatment Update
of the 11th IAS Conference on HIV Science (Virtual)
Thursday, September 23, 2021 | 6:00 PM - 8:30 PM Central Time

Guest Speakers

“Overview of HIV and COVID-19 Epidemiology”
Catherine Creticos, MD, Clinical Director-Illinois
Midwest AIDS Training + Education Center

“Ending the HIV Epidemic in the Current Socio-political and Public Health Environment”
Darrell Wheeler, PhD, MPH, ACSW
Provost & Senior Vice President for Academic Affairs, Iona College, NY

“HIV Clinical Update”
Joseph J. Eron, MD
Professor of Medicine & Chief, Infectious Diseases Division, UNC at Chapel Hill
Thank You!

Please complete your evaluation.

1. Link in the chat box
2. Scan the QR Code
3. Link in your email