ACTHIV 2018: A State-of-the-Science Conference for Frontline Health Professionals
Cancer screenings for the HPV Clinician: Human papillomavirus

ACTHIV 2018, Chicago

Timothy Wilkin, M.D. MPH
Associate Professor of Medicine
Division of Infectious Diseases
Learning Objectives

• Review the current approach to anal cancer screening
• Discuss epidemiology of HPV-associated oropharyngeal cancer and implications for clinical practice
• Review current data on HPV vaccination for people living with HIV
Worldwide HPV-related Disease Burden: 630,000 Cancer Cases in Men and Women

- Penile cancer: 13,000 (Male: 13,000, Female: 21,000)
- Vulvar & vaginal cancer: 21,000 (Male: 13,000, Female: 21,000)
- Oropharyngeal cancer: 28,200 (Male: 28,200, Female: 7,500)
- Anal cancer: 17,000 (Male: 17,000, Female: 18,000)
- Cervical cancer: 530,000
- High-grade cervical dysplasia: 21,900,000
- Low-grade cervical dysplasia: 17,900,000
- Genital warts: 17,300,000 (Male: 17,300,000, Female: 14,700,000)

≈ x 60 fold

*Estimated 90% of high-grade cervical lesions are HPV related; †Estimated 73% of low-grade cervical lesions are HPV related; ‡Estimated gender ratio of genital warts: 54% males; 46% females

Anal Cancer
Anal Cancer in HIV+ people

Schim van der Loff, HIV AIDS Curr Report 2014
Anal Cancer in HIV+ people

Cerv CA prior to pap

Current cerv CA in US

Schim van der Loff, HIV AIDS Curr Report 2014
Natural History of HPV Infection and Potential Progression to Anal Cancer

0–1 Year

Initial HPV Infection

Higher HPV exposure

0–5 Years

Continuing Infection

Anal LSIL

1–20 Years

Anal HSIL

Invasive Anal Cancer

Cleared HPV Infection

Decreased cell-mediated immunity

Prevention of Anal Cancer

Prevention of Anal Cancer

Cleared HPV Infection

0–1 Year

Initial HPV Infection

0–5 Years

Continuing Infection

Anal LSIL

1–20 Years

Anal HPV

Invasive Anal Cancer

Anal cancer prevention

- Goal is to identify pre-cancerous areas of the anus that can be removed to prevent invasive cancer
  - **SCREEN** with cytology (or HPV testing *not FDA approved)
  - **DIAGNOSE HSIL** with High Resolution Anoscopy
  - **TREAT HSIL** with ablation or topical therapy
- Anal cancer is treated with combined chemotherapy and radiation

*Expert opinion, Chin-Hong, *CID*, 2003
Personnel to perform anal cancer screening

- Cytology
  - MD, NP, PA, RN
- High resolution anoscopy
  - MD (any speciality), NP, PA
  - American Society for Colposcopy and Cervical Pathology offers HRA course
  - Preceptorship, Observation in clinic is best
  - Steep learning curve; 50–100 procedures required

Treatment of anal HSIL
- HRA providers should add this on once comfortable with HRA
ARS #1: Which of these is the recommended way to prevent anal cancer according to national guidelines?

- A. Treatment of anal condyloma
- B. HPV vaccination prior to sexual activity
- C. Screening and treatment of anal HSIL
- D. HPV vaccination of sexually active adults
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## Anal HSIL in HIV-infected women

<table>
<thead>
<tr>
<th>Anal Cytology</th>
<th>Anal Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) of Total</td>
</tr>
<tr>
<td></td>
<td>N=255</td>
</tr>
<tr>
<td>Normal</td>
<td>101 (40%)</td>
</tr>
<tr>
<td>ASCUS/LSIL</td>
<td>129 (50%)</td>
</tr>
<tr>
<td>ASC-H/HSIL</td>
<td>25 (10%)</td>
</tr>
</tbody>
</table>

Note: 8 were unevaluable for anal cytology, including 3 with HSIL

Prevalent histologic anal HSIL: 28%

Stier E, HPV 2017, CT02
**AMC-076: Randomized, clinical trial of infrared coagulation of anal HSIL**

<table>
<thead>
<tr>
<th></th>
<th>IRC</th>
<th>Control</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall CR Rate</strong></td>
<td>63% (38/60)</td>
<td>27% (16/60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>95% CI, 50-75%</td>
<td>95% CI, 16-40%</td>
<td></td>
</tr>
<tr>
<td><strong>Overall CR/PR Rate</strong></td>
<td>75% (45/60)</td>
<td>43% (26/60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>95% CI, 62-85%</td>
<td>95% CI, 31-57%</td>
<td></td>
</tr>
<tr>
<td><strong>PR rate for those not achieving CR</strong></td>
<td>32% (7/22)</td>
<td>23% (10/44)</td>
<td>0.247</td>
</tr>
<tr>
<td></td>
<td>95% CI, 14-55%</td>
<td>95% CI, 11-38%</td>
<td></td>
</tr>
</tbody>
</table>

* One-sided stratified Mantel-Haenszel chi-square test.
  Strata were Laser Surgery Center (n=71) and remaining 5 sites (n=49).
Controversies in anal cancer screening

• General acceptance that anal HSIL precedes anal cancer, but anal HSIL is highly prevalent.
• Most people with anal HSIL will never develop cancer.
• Treatment for anal HSIL is not well studied and are clearly less effective than those for cervical HSIL
  – Recurrent HSIL is the norm; multiple treatments are usually needed to clear HSIL
• Accessing high resolution anoscopy and treatment for anal HSIL is difficult
• Not yet recommended by organizations setting standards for health care maintenance
  – Cost effectiveness is unclear
  – No consensus on whether to include all women and men with HIV
• No data that treating anal HSIL will reduce the risk of anal cancer
ANCHOR TRIAL

Screen > 17,385

Enroll 5,058

Retain for 5-8 years

Estimated < 50 develop cancer

anchorstudy.org; NCT02135419; Sponsor: NCI
ARS #2: Which of these statements is false?

- A. The HPV type responsible for most HPV-related oropharyngeal cancers (OPC) is HPV 16
- B. Men are more likely than women to develop OPC
- C. HIV-infected populations are more likely to develop OPC cancer than HIV-uninfected populations
- D. HPV related OPC can be prevented in most people through active screening
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Oropharyngeal Cancer
Oropharyngeal Cancer (OPC)

70% HPV-related

85% HPV 16

94% of HPV-related OPC are caused by HR-HPV in 9-valent HPV vaccine

Saraiya M et al JNCI 2015
HPV-Related OPC Incidence is Higher in Men

HPV-associated OPC is 2-3 times higher among people living with HIV

There are no accepted screening or prevention modalities for prevention of HPV-related OPC
How can we reduce HPV-related cancers in people living with HIV
Active screening?

• Anal cancer may be a viable target for active screening
  – Need results from ANCHOR
  – Need improved treatments of anal HSIL
  – Therapeutic vaccines, direct acting anti-HPV drugs

• Anal cancer screening is unlikely to be implemented in resource constrained settings
  – Health care resources better spent on HPV vaccine campaigns
  – Cervical cancer screening programs need strengthening
  – Epidemiology of anal cancer not well described
  – Treatment of anal HSIL involves multiple visits and significant resources

• No screening programs exist for OPC
  – HPV vaccination is best hope for prevention of HPV-related OPC
Prevention of Anal Cancer with HPV vaccination

Excludes those baseline vaccine infection

Includes those baseline vaccine infection

Palefsky, NEJM 2011
HPV vaccination: ACTG A5298 Study Design

- HIV+ ≥27 yrs
- No HPV cancers
- All CD4/RNA
- RAI for men

→ RANDOMIZE: stratify by HSIL, sex, site

→ 4vHPV or placebo: 0, 8, 24

→ Anal HPV oral HPV

Cyto: q6 mo

HSIL tx by local standard; HRA providers certified

Wilkin T, CID 2018, accepted
### ACTG A5298: HPV vaccine in HIV+ >27 yrs

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

Wilkin T, CID 2018, accepted
HPV16/18 VE at Non-Cervical Sites
Costa Rica Vaccine Trial
One-time detection of HPV16/18 infection 4 yrs. after vaccination

1Herrero R et al. PLOS ONE 2013; 2Kreimer AR et al Lancet Oncology 2011

Slide courtesy of A Kreimer
Strong Association Between Serum and Oral HPV Antibodies Among Vaccinated Men

HPV16
Correlation between Serum AB and Oral Gargle AB at Month 7

Spearman's Rho = 0.8432 p<0.0001
Prevalence of oral HPV by vaccine status: NHANES 2011-2014

Desmukh KS, Annals of Internal Medicine, 2017
VLP Vaccines

- **GSK**
  - **Cervarix**
    - HPV 16 and 18
    - Insect cells
    - Aluminum and TLR 4 agonist adjuvant
    - im injection at 0, 1, 6 months
  
- **Merck**
  - **Gardasil**
    - HPV 6, 11, 16, 18
    - Yeast
    - Aluminum adjuvant
    - im injection at 0, 2, 6 months
  - **Gardasil-9**
    - adds 31, 33, 45, 52, 59

*These 9 types cause 90% of HPV-related cancers!!!
ACIP HPV vaccine recommendations

- **Females**
  - Routine vaccination of 11-12 girls
  - Catch-up vaccination up to age 26

- **Males**
  - Routine vaccination of 11-12 boys
  - Catch-up vaccination up to age 21
  - Routine vaccination of HIV+ males, other immunosuppressed males, men who have sex with men through age 26

- **Dosing schedule**
  - Two doses (0 and 6 months) when starting prior to age 15
  - Three doses (0, 1-2, 6 months) after age 15 and if having any immune suppression.

Meites E et al, MMWR, 2016
Real world evidence of HPV vaccine efficacy

Trends in histologically confirmed high-grade cervical intraepithelial neoplasia
Fall in cervical HPV prevalence in young women 18-24 yrs

Decline in Genital Warts <30 years of age

Percentage testing positive

- <21 years
- 21-30 years
- >30 years

Year

2004 2005 2006 2007 2008 2009 2010 2011

Females <21 years 92.6% decline post vaccination
Females 21-30 yrs 72.6% decline post vaccination
START study: Hazard ratio for infection-related cancer

Immediate ART reduced infection-related cancer by 76% (95% CI 36%-89%)
Early ART reducing Anal Cancer

Blaser N, AIDS, 2017
## Statin exposure and risk of cancer

### Death rate 45% lower with statin use

### Statin use associated with significant protection against HPV cancers

### Table: Effect of statin use on cancer risk

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>All Participants</th>
<th>Uninfected</th>
<th>HIV +</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Cancer</td>
<td>0.61 (0.56 – 0.67)</td>
<td>0.65 (0.59 – 0.72)</td>
<td>0.51 (0.40 – 0.64)</td>
<td>0.051</td>
</tr>
<tr>
<td>AIDS-Defining Cancers</td>
<td>0.31 (0.18 – 0.53)</td>
<td>0.39 (0.16 – 0.95)</td>
<td>0.28 (0.06 – 1.29)</td>
<td>0.8</td>
</tr>
<tr>
<td>Non-AIDS Defining Cancers</td>
<td>0.63 (0.58 – 0.69)</td>
<td>0.67 (0.60 – 0.74)</td>
<td>0.53 (0.41 – 0.67)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

### Table: Virus-related cancers

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>All</th>
<th>Uninfected</th>
<th>HIV +</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal</td>
<td>0.62 (0.45 – 0.86)</td>
<td>0.82 (0.55 – 1.24)</td>
<td>0.28 (0.10 – 0.82)</td>
<td>0.1</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>0.35 (0.18 – 0.67)</td>
<td>0.24 (0.08 – 0.72)</td>
<td>0.49 (0.08 – 3.06)</td>
<td>0.6</td>
</tr>
<tr>
<td>Liver</td>
<td>0.62 (0.45 – 0.86)</td>
<td>0.82 (0.55 – 1.24)</td>
<td>0.28 (0.10 – 0.82)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>0.43 (0.15 – 1.25)</td>
<td>N/A</td>
<td>1.00 (0.14 – 7.10)</td>
<td>.</td>
</tr>
<tr>
<td>NHL</td>
<td>0.29 (0.16 – 0.54)</td>
<td>0.36 (0.14 – 0.91)</td>
<td>0.30 (0.05 – 1.63)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Bedimo, 2018 CROI Abstract 132**
Summary

• Anal cancer is a common cancer in HIV-infected populations
• Screening for anal cancer should be considered for HIV-infected populations
  o Data to support this are limited
  o Further study is needed
• HPV vaccination is the best hope for prevention of HPV-related cancers
• Emerging data support efficacy of vaccination against HPV-related oropharyngeal cancer
  o Need for efficacy trial to definitively prove efficacy?
• World-wide push for early initiation of ART (e.g. WHO 90-90-90) should lead to reduced incidence of HPV-related cancer
Acknowledgments

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  National Cancer Institute
  National Institute of Allergy and Infectious Diseases
  National Institute of Dental and Craniofacial Research
Post test question

ARS #3: Which of the following groups are not recommended for HPV vaccination according to ACIP?

- A. HIV-infected girls age 11-12
- B. HIV-infected boys age 11-12
- C. MSM up to age 26 if not previously vaccinated
- D. HIV-infected women age 27-45 with negative hrHPV tests
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