HPV-Related Malignancies in HIV Patients

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Carrie Kovarik, MD
Dermatologic Manifestations of HIV and AIDS Forum AAD 2019

I do not have any relevant relationships with industry.
Question #1
Which malignancy has the highest *standard incidence ratio* in patients with AIDS < 50 yrs old?

(*SIR* = ratio of observed # of cancer cases in a group to the expected # of cases)

A. Head and neck cancer
B. Anal cancer
C. Melanoma
D. Liver cancer
E. Lung Cancer
Which malignancy has the highest *standard incidence ratio* in patients with AIDS < 50 yrs old? 

(SIR = ratio of observed # of cancer cases in a group to the expected # of cases)

A. Head and neck cancer
B. Anal cancer
C. Melanoma
D. Liver cancer
E. Lung Cancer
The Rising Challenge of Non–AIDS-Defining Cancers in HIV-Infected Patients

John F. Deeken,1 Angelique Tjen-A-Looi,2 Michelle A. Rudek,4 Catherine Okuliar,3 Mary Young,2 Richard F. Little,5 and Bruce J. Dezaubé6

- Cancers not previously associated with HIV/AIDS are increasing in incidence.
- These *non–AIDS-defining cancers* (NADCs) include cancers of the lung, liver, kidney, anus, head and neck, skin, Hodgkin’s lymphoma, & others.
- In populations benefiting from ART, some NADCs have a *higher relative incidence* compared with the same cancer rates seen in the general population, even after controlling for known cancer risk factors.
Non–AIDS-defining cancers (not KS, NHL, cervix) are the leading non–AIDS-related causes of death in the late HAART era, among both people with HIV and people with AIDS (PWA).

Significant excess mortality emerged for cancers associated with viruses, for which HIV-infected individuals are likely to lose the immune control of infections, and for cancers associated with unhealthy behaviors, such as tobacco smoking.
The Rising Challenge of Non–AIDS-Defining Cancers in HIV-Infected Patients

Table 1. Standard Incidence Ratios of Selected Non–AIDS-Defining Cancers [2, 5–8]

<table>
<thead>
<tr>
<th>Non–AIDS-Defining Cancer</th>
<th>Cancer Risk (Standardized Incidence Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal</td>
<td>33.4–42.9</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>14.7–31.7</td>
</tr>
<tr>
<td>Liver</td>
<td>7.0–7.7</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma/Basal cell</td>
<td>3.2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1.1–2.6</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>1.0–4.1</td>
</tr>
<tr>
<td>Lung</td>
<td>2.2–6.6</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2.2–2.5</td>
</tr>
<tr>
<td>Renal</td>
<td>1.8–2.2</td>
</tr>
<tr>
<td>Cancer Site/Type (ICD-10 Codes)*</td>
<td>Total (14,180 Person-Years)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td>Obs./Exp.</td>
</tr>
<tr>
<td>AIDS-defining</td>
<td>282/0.7</td>
</tr>
<tr>
<td>Kaposi sarcoma (C46)</td>
<td>63/&lt;0.1</td>
</tr>
<tr>
<td>Cervix uteri (C53)</td>
<td>6/&lt;0.1</td>
</tr>
<tr>
<td>Non–Hodgkin lymphoma (C82–88, C96)</td>
<td>221/0.6</td>
</tr>
<tr>
<td>Non–AIDS-defining†‡</td>
<td>127/17.3</td>
</tr>
<tr>
<td>Head and neck (C00–14, C30–32)</td>
<td>9/1.1</td>
</tr>
<tr>
<td>Stomach (C16)</td>
<td>4/1.2</td>
</tr>
<tr>
<td>Colon-rectum (C18–20)</td>
<td>10/1.8</td>
</tr>
<tr>
<td>Anus (C21)</td>
<td>5/&lt;0.1</td>
</tr>
<tr>
<td>Liver and bile ducts (C22)</td>
<td>17/1.3</td>
</tr>
<tr>
<td>Bronchus and lung (C34)</td>
<td>38/4.7</td>
</tr>
<tr>
<td>Skin melanoma (C43)</td>
<td>4/0.4</td>
</tr>
<tr>
<td>Uterus, not otherwise specified (C55)</td>
<td>4/&lt;0.1</td>
</tr>
<tr>
<td>Hodgkin lymphoma (C81)</td>
<td>12/&lt;0.1</td>
</tr>
<tr>
<td>Leukemia (C91-95)</td>
<td>5/0.7</td>
</tr>
</tbody>
</table>
Younger ages at diagnosis were observed for PLWH compared with general population for lung, anal, oral cavity/pharynx, kidney cancers and myeloma.
<table>
<thead>
<tr>
<th>Cancer</th>
<th>Observed in HIV-Infected Individuals</th>
<th>Observed in General Population</th>
<th>General Population After Weighting&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Median Age, y</td>
<td>Median Age, y</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Lung</td>
<td>644</td>
<td>54</td>
<td>68</td>
</tr>
<tr>
<td>Prostate</td>
<td>504</td>
<td>58</td>
<td>66</td>
</tr>
<tr>
<td>Anus</td>
<td>291</td>
<td>47</td>
<td>57</td>
</tr>
<tr>
<td>Liver</td>
<td>226</td>
<td>54</td>
<td>62</td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td>173</td>
<td>51</td>
<td>60</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>171</td>
<td>44</td>
<td>39</td>
</tr>
<tr>
<td>Colon</td>
<td>111</td>
<td>55</td>
<td>67</td>
</tr>
<tr>
<td>Kidney</td>
<td>109</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>Larynx</td>
<td>86</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td>Melanoma (whites only)</td>
<td>77</td>
<td>49</td>
<td>56</td>
</tr>
<tr>
<td>Breast</td>
<td>56</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td>Pancreas</td>
<td>55</td>
<td>53.5</td>
<td>67</td>
</tr>
<tr>
<td>Myeloma</td>
<td>49</td>
<td>52</td>
<td>66</td>
</tr>
</tbody>
</table>
Human Papillomavirus (HPV) Related Malignancy in HIV
Human papillomavirus–related genital disease in the immunocompromised host

Part I

Rachel H. Gormley, MD,1 and Carrie L. Kovarik, MD2,3
Philadelphia, Pennsylvania

CAPSULE SUMMARY

- Human papillomavirus causes both benign condyloma acuminata and anogenital malignancies.
- Immunosuppressed patients, including patients with HIV infection and organ transplant recipients, are at increased risk for developing these conditions.
- Patients with HIV infection and organ transplant recipients require heightened screening and aggressive treatment.
Perspective of HPV Related Skin Disease

- Immune status has a significant impact on HPV disease course & response to treatment
- *Increased rates* of HPV infection, with increased duration/persistence in HIV
- *Increasing susceptibility* to new HPV infection + HIV ↑ reactivation of latent virus and hastens the course of established HPV infections

Persistence of HPV Related Skin Disease

**Beneficial effect of HAART may be less pronounced** when HPV has progressed with HIV, because:

- HPV-specific immunity has been irreversibly damaged, or
- HPV related changes have persisted long enough the sufficient genetic changes have accumulated by the time of HAART initiation

Spectrum and progression of disease from condyloma to aggressive anogenital squamous cell carcinoma in 3 HIV-positive patients

Olaf Rodriguez, BS,² and Carrie L. Kovarik, MD²,³

Philadelphia, Pennsylvania
21yo HIV positive female on HAART (CD4 183) with genital warts not responding to cryotherapy
45 yo HIV + female with biopsy proven SCCIS on the left inner thigh, needing scouting biopsies to rule out invasive SCC
Perianal Bowen Disease in a Child with Human Immunodeficiency Virus

Kathleen A. Carroll, M.D.,* Jeffrey Pierce, M.D.,† and Carrie L. Kovarik, M.D.‡

Squamous Cell Carcinoma in situ
41 yo female HIV + (CD4 952) with large verrucous macerated plaque

Biopsy showed SCCIS
Question #2
In this patient, what is the next step that may help the patient have the best outcome?

A. Surgical excision/vulvectomy
B. Scouting biopsies
C. Radiation
D. Imiquimod therapy
E. HPV Vaccination
In this patient, what is the next step that may help the patient have the best outcome?

A. Surgical excision/vulvectomy
B. **Scouting biopsies**
C. Radiation
D. Imiquimod therapy
E. HPV Vaccination
38 yo female, HIV+, history of cervical cancer s/p hysterectomy and 2 year history of “ulcers” on the perineum

Invasive Squamous Cell Carcinoma
Invasive Squamous Cell Carcinoma
59 yo HIV + CD4 450, on HAART, growing over the last 2-3 years since circumcision.
Invasive Squamous Cell Carcinoma
Clearance of HPV infection, including infection with oncogenic types, was slower in the glans/coronal sulcus of the penis of uncircumcised men than circumcised men.

From: Reduced Clearance of Penile Human Papillomavirus Infection in Uncircumcised Men
J Infect Dis. 2010;201(9):1340-1343. doi:10.1086/651607
53yo HIV(+) with CD4 count 600's & a few month history of friable nodular exophytic penile plaque with surrounding verrucous change

Invasive Squamous Cell Carcinoma
Squamous Cell Carcinoma

Penile Cancer

Vulvar Cancer

Courtesy of Dr. Justin Finch
Human Papillomavirus and Genital Warts: A Review of the Evidence for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines

Ina U. Park,¹,² Camille Introcasa,² and Eileen F. Dunne²,³

- **Anal cancer** is rare in gen population (1–2 cases/100 000 PY), but burden is much **higher among MSM**
  - Anal cancer incidence HIV-neg MSM = 5 cases/100 000 PY
  - Anal cancer incidence HIV-pos MSM = 45.9 cases/100 000 PY

- Anal HPV is nearly ubiquitous in HIV+ MSM (93%), with
  - *High-risk HPV prevalence* = 73.5% for HIV-pos MSM
  - High-risk HPV prevalence = 37.2% for HIV-neg MSM
Human Papillomavirus and Genital Warts: A Review of the Evidence for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines

Ina U. Park,1,2 Camille Introcasa,2 and Eileen F. Dunne3,4

- >½ of HIV+ MSM have abnormal cytology (57%), and 29% have HSIL
- Incidence of HSIL among HIV+ MSM ranges from 8.5-15.4% PY
Distribution of HPV Genotype in Anal Condyloma (CA): Higher Prevalence of HR-HPV in MSM with HIV

- **Prevalence of HR-HPV:**
  - HIV+ MSM (70.4%)
  - HIV-negative MSM (33.3%, $P=0.0311$)
  - HIV-negative MSW (18.8%, $P=0.0016$).

- Logistic regression showed *HIV*+ as primary risk factor for HR-HPV infection in CA.

- **HSIL was detected in 25% of CA from HIV+ MSM** (25.9%), compared to none in HIV-negative MSW (0.0%, $P=0.0346$).

- *Surveillance* is a necessity for the HIV+ MSM population!
Higher Prevalence of HR HPV in MSM with HIV Infection

Figure 1. Distribution of HPV genotypes in CA patients. (A) Distribution of HPV genotypes in overall CA patients or CA patients with or without HIV infection.
• **745 HIV+ women** were screened with anal cytology.
• 15-39% had abnormal anal cytology
• 208 underwent HRA following abnormal anal cytology: **HSIL found in 18-26%** of anal biopsies
• **Cigarette smoking** > doubled HSIL risk.
• Neither meeting criteria for screening nor history of receptive anal sex was significantly associated with HSIL.

![Table 3. Anal Cytology Results Preceding High-Resolution Anoscopy Evaluation Compared to High-Resolution Anoscopy Results](image)

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Benign</th>
<th>LSIL/Condyloma</th>
<th>HSIL/Cancer</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ASCUS</td>
<td>70 (92)</td>
<td>48 (58)</td>
<td>31 (63)</td>
<td></td>
</tr>
<tr>
<td>ASC-H</td>
<td>0 (0)</td>
<td>4 (5)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>LSIL</td>
<td>6 (8)</td>
<td>29 (35)</td>
<td>7 (14)</td>
<td></td>
</tr>
<tr>
<td>HSIL</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>10 (21)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ASC-H: atypical squamous cells, cannot rule out HSIL; ASCUS: atypical cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.
High-grade Dysplasia in Anogenital Warts of HIV-Positive Men

Alexander Kreuter, MD; Christos Siorokos, MD; Frank Oellig, MD; Steffi Silling, PhD; Herbert Pfister, PhD; Ulrike Wieland, MD

Key Points

**Question** Do anogenital lesions of HIV-positive men that clinically appear as benign warts contain areas of dysplasia, and if so, what are the virological characteristics of those lesions?

**Findings** In this case series, a high proportion of anogenital warts contained areas of high-grade and low-grade dysplasia or even invasive cancer. Some of these lesions contained only low-risk-HPV types. Dysplasia was absent in all lesions of immunocompetent control patients.
High-grade Dysplasia in Anogenital Warts of HIV-Positive Men

Alexander Kwock, MD; Christos Siorokos, MD; Frank Owlig, MD; Steffi Sillig, PhD; Herbert Pfister, PhD; Ulrike Wieland, MD

Box. Recommendations for the Diagnosis and Treatment of Anogenital Warts in HIV-Positive Men

**Clinical Examination**
1. Clinical inspection of the entire anogenital area
2. Documentation of size and location of anogenital warts (AGWs) and search for clinical signs of dysplasia (e.g., punctuation, mosaicism, neovascularization/abnormal vessels)
3. Perform (or send patient to) high-resolution anoscopy to exclude anal intraepithelial neoplasia and/or anal carcinoma
4. Obtain biopsy specimens of representative lesions

**Histopathological Examination**
1. Perform routine histopathological examination (standard fixation with hematoxylin-eosin staining)
2. In case of histopathological signs for dysplasia, add immunohistochemical staining for Ki67 and p16
3. Optional: add HPV genotyping in case of signs of dysplasia in histopathology

**Treatment**
1. Perform ablative treatment of AGWs (e.g., electrocautery, infrared coagulation, surgical excision)
2. Consider additional treatment with imiquimod 5% cream

*Anal AGWs represent a risk factor for AIN and anal carcinoma*
Question #3
This carcinoma is most often associated with which HPV type?

A. HPV 6
B. HPV 16
C. HPV 18
D. HPV 31
E. HPV 73
This carcinoma is most often associated with which HPV type?

A. HPV 6
B. HPV 16
C. HPV 18
D. HPV 31
E. HPV 73
Digital squamous cell carcinoma and association with diverse high-risk human papillomavirus types

Rachel H. Gormley, BS,a Caroline M. Groft, MD, PhD,a Christopher J. Miller, MD,a
and Carrie L. Kovarik, MD,a,b
Philadelphia, Pennsylvania

- Digital squamous cell carcinoma (SCC) is rare and often mimics benign conditions, making it a diagnostic challenge.
- Digital SCC is often associated with high-risk, oncogenic human papillomavirus subtypes.
- Although the majority of previously published reports have implicated human papillomavirus-16, a variety of high-risk oncogenic subtypes, including human papillomavirus-16, -33, -51, and -73, may be associated with digital SCC.
- Digital SCCs often recur and aggressive treatment is recommended.
Case report

Human papillomavirus type 73 associated with multiple cutaneous squamous cell carcinomas in an immunosuppressed patient

Camille E. Introcaso¹, MD, Peter L. Rady², MD, PhD, Qin He², MD, Stephen K. Tyring³, MD, PhD, MBA, and Carrie L. Kovarik¹⁴, MD
Oral HPV in HIV Patients

Treatment of oral condylomata acuminata in a HIV-1 patient with bleomycin

Leonor Girão, Isabel França, Helena Macedo, Carmo Ornelas, Moura Nunes, Carlos Araújo, Kamal Mansinho

JEADV (2000) 14, 313—333
Spectrum and progression of disease from condyloma to aggressive anogenital squamous cell carcinoma in 3 HIV-positive patients

Olaf Rodriguez, BS, and Carrie L. Kovarik, MD

Philadelphia, Pennsylvania

Fig 3. HPV-related oral leukoplakia with biopsy-proven invasive squamous cell carcinoma. This is the clinical appearance before Mohs surgery (A) and after clearance of the tumor (B).
Oral Human Papillomavirus in Men Having Sex with Men: Risk-Factors and Sampling

Tim R. H. Read¹,², Jane S. Hocking³, Lenka A. Vodstrcil¹,², Sepehr N. Tabrizi⁴, Michael J. McCullough⁵, Andrew E. Grulich⁶, Suzanne M. Garland⁴, Catriona S. Bradshaw¹,⁷, Marcus Y. Chen¹,², Christopher K. Fairley¹,²

Table 1. Prevalence of oral HPV types, by HIV status, in 500 men who have sex with men.

<table>
<thead>
<tr>
<th>HPV type</th>
<th>HIV negative N = 251 n (%), 95% CI</th>
<th>HIV positive N = 249 n (%), 95% CI</th>
<th>Prevalence ratio¹</th>
<th>Overall n (%), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any HPV type</td>
<td>17 (7, 4–11)</td>
<td>48 (19, 15–25)</td>
<td>2.8</td>
<td>65 (13, 10–16)</td>
</tr>
<tr>
<td>HPV 16</td>
<td>2 (0.8, 0.1–3)</td>
<td>11 (4, 2–8)</td>
<td>5.5</td>
<td>13 (3, 1–9)</td>
</tr>
<tr>
<td>High risk HPV types ²</td>
<td>5 (2, 0.6–5)</td>
<td>20 (8, 5–12)</td>
<td>4.0</td>
<td>25 (5, 3–7)</td>
</tr>
<tr>
<td>HPV³ types 6 or 11 or 16 or 18</td>
<td>5 (2, 0.6–5)</td>
<td>16 (6, 4–10)</td>
<td>3.2</td>
<td>21 (4, 3–6)</td>
</tr>
<tr>
<td>More than 1 type of HPV</td>
<td>3 (0.6, 0.2–3)</td>
<td>18 (7, 4–11)</td>
<td>6.0</td>
<td>21 (4, 3–6)</td>
</tr>
</tbody>
</table>

CI confidence interval
¹) Ratio of prevalence in HIV-positive to HIV-negative MSM.
²) One or more of types 16, 18, 31, 33, 39, 45, 51, 56, 58, 59, 68 which are considered oncogenic in the cervix.
³) Included in the quadrivalent vaccine.

doi:10.1371/journal.pone.0049324.t001
Other HIV/HPV Related Skin Disease

Extensive Flat Warts
First evidence of an association between HPV and non-melanoma skin cancer comes from patients with EDV

EDV is a rare heritable disease characterized by cutaneous warts that display not only a high rate of progression to SCC on sun-exposed sites, but also a strong predisposition to infection by b-HPVs, for which HPV 5 and 8 predominate.

Two EV genes (EVER1 and EVER2) identified

Variant genotype in this study was related to SCC risk [adjusted OR for homozygous variant versus homozygous wild type for the EVER2 polymorphism 1.7, 95% CI 1.1–2.7].
Acquired Epidermodysplasia Verruciformis Syndrome in HIV-Infected Pediatric Patients: Prospective Treatment Trial With Topical Glycolic Acid and Human Papillomavirus Genotype Characterization

ARCH DERMATOL

![Bar chart showing HPV type distribution](chart.png)
• **HPV 16/18 vaccine** potentially prevents the majority of invasive cervical (66.2%), anal (79.4%), oropharyngeal (60.2%), and vaginal (55.1%) cancers, as well as many penile (47.9%), vulvar (48.6%) cancers: 24,858 cases annually.

• **The 9-valent vaccine** also targeting HPV 31/33/45/52/58 may prevent an additional 4.2% to 18.3% of cancers: 3,944 cases annually.

• **Younger age** at diagnosis was associated with higher HPV 16/18 prevalence (for most cancers).
Conclusions: In the United States, current vaccines will reduce most HPV-associated cancers; a smaller additional reduction would be contributed by the new 9-valent vaccine.
Questions?