HPV-related cancers and their prevention in women

Deborah Konopnicki
Saint-Pierre University Hospital
Université Libre de Bruxelles

deborah.konopnicki@stpierre-bru.be
Disclosure

• Presenter: D. Konopnicki
  – Travels and congress Grants from Pfizer, ViiV and MSD.
  – Fee as invited speaker from Janssens.
  – No conflicts of interest.
Women living with HIV according to UNAIDS and ECDC in 2012

400,000 women living with HIV

7,500 new diagnosis of HIV in women
Agenda

- HPV and cancer
- The burden of HPV in HIV-positive patients
- Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-positive women
What are the HPV-induced cancers?

- Cervix: 99%
- Anus: 84%
- Vagina: 70%
- Vulva: 40%
- Oro-pharyngeal: 35%

High risk HPV (HPVHR): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
Persistent Infection

5-10% If HIV negative

20-30% If HIV positive
Agenda

- HPV and cancer

- The burden of HPV in HIV-positive patients

- Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-positive women
The burden of HPV infections and induced lesions in HIV-positive patients

• **HPV Infection**
  - Prevalence and incidence of HPV infection are higher.
  - HPV viral load are higher. More infections with multiple genotypes.
  - Clearance is decreased and recurrence of latent infection are frequent.
  - Persistent infection is significantly higher.

• **Precancerous lesions**
  - Prevalence and incidence of precancerous lesions are higher.
  - Spontaneous regression are less frequent.
  - Recurrence after treatment are more frequent.

• **Cancer**
  - Incidence 6-10 times higher for the cervix
  - Incidence 40 times higher for the anus
Infection by HPV and HPV-induced lesions in the cervix in HIV-positive women

• **High risk HPV**
  - Prevalence: **43 %** vs. **12%** (Belgium: n=652,38 y)
  - Prevalence: **33.2%** (Spain: n=479,42 y)
  - Prevalence: **49.5%** (MACH-1:n=518,35y)
  - Incidence: **13.4%** vs. 5 % women-year

• **Cervical dysplasia**
  - Prevalence of abnormal cytology: **38%** vs. **16%**
  - Prevalence in Belgium: All AC **28%** vs. 5.9%
  - Prevalence in MACH-1 AAC /HSIL **36%/8%**
  - Prevalence in Spain: HSIL **3.8%**
  - Incidence of abnormal cytology: **20%** vs. 5 % after 3
  - Incidence in Belgium: ACC **6% women year**
  - Incidence in Belgium: HSIL **1.4% women year**

• **After conisation:**
  Abnormal cytology after conisation **66%** vs. **33%**

---

1 Konopnicki D. PhD June 2014
2 Stuardo V. PLOS one 2012
3 Heard I. BJOG 2012
## Epidemiology in HIV-positive patients

Study over 500,000 HIV patients linked with cancer registry data in US

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anus (men MSM)</strong> AIN3/ Invasive</td>
<td>90/52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anus (men MSW)</strong> AIN3/ Invasive</td>
<td>21/14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anus (women)</strong> AIN3 / Invasive</td>
<td>33/15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cervix</strong> CIN3/ Invasive</td>
<td>9/6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Penis</strong> PIN3/ Invasive</td>
<td>20/5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vagina or Vulva</strong> Va VIN3/ Invasive</td>
<td>27/6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anus (men)</strong> AIN3 Invasive (1)</td>
<td>1.7</td>
<td>10.5</td>
<td>18.3</td>
<td>29.5</td>
</tr>
<tr>
<td><strong>Anus (women)</strong> AIN3 Invasive (1)</td>
<td>0</td>
<td>0</td>
<td>1.7</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Cervix</strong> CIN3 Invasive (50)</td>
<td>178</td>
<td>71</td>
<td>449</td>
<td>90</td>
</tr>
<tr>
<td><strong>Oropharynx</strong> (3)</td>
<td>0</td>
<td>3.9</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>Penis</strong> PIN3 Invasive (1.5)</td>
<td>1.7</td>
<td>0</td>
<td>1.7</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Vagina or Vulva</strong> Va/VIN3 Invasive (3)</td>
<td>17</td>
<td>54</td>
<td>60</td>
<td>8</td>
</tr>
</tbody>
</table>

Agenda

- HPV and cancer
- HPV and HIV interactions
- The burden of HPV in HIV-positive patients

- Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-positive women
Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-positive women
Cervical screening in developed countries

Pap-smear +/- HPV-DNA

- Normal
- Ascus
- LSIL
- HSIL

HPV neg
- Check after 1 year
- Normal
- Pap-smear after 6 months

HPV pos
- Check after 6 months
- Colposcopy + biopsy
- LG CIN
- HG CIN
- Conisation

Abnormal cells present
Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow up of four European randomised controlled trials

Ronco G. The lancet 2014.
Cervical screening in developed countries

Pap-smear +/- HPV-DNA

- Normal
- Ascus
- LSIL
- HSIL

HPV neg
- Check after 1 year
  - Normal

HPV pos
- Check after 6 months
  - LG CIN
    - Pap-smear after 6 months
    - Colposcopy + biopsy after 1 year
    - Conisation
  - HG CIN
  - Colposcopy + biopsy
Cervical screening in developed countries

Could this be applied to HIV-positive women?

- Under 30 years HPV prevalence is too high
- After 30 years:
  - HPV testing is **cost-effective** in HIV-women
  - It has a good **Negative Predictive Value** for women with CD4 > 500/μL.

These women could be screened at longer interval.


---

**Normal**

- Check after 1 year

**Colposcopy + biopsy after 6 months**

- According to age and CD4

**LG CIN**

- Check after 6 months/3 years

**Conisation**

**HG CIN**
Screen and treat approach in limited resource setting

Cervical Cancer Prevention in HIV-infected women using the « see and treat » approach: Testing for HRHPV; results after 2 hours which allows treatment the very same day in

- South Africa Kuhn and al. AIDS 2010
- Botswana Ramogola-Masire D. J Acqui Immune Def Syndr 2012
- India Joshi S. AIDS 2013
Screening for cervical cancer in developed countries

- Refer for screening at the first consultation

- If ≥30 years
  - Test for HRHPV
    - If HPV positive: colposcopy/biopsy
    - If HPV negative: next screen can be after
      - 3-5 years if CD4 high (>500/µL) and under cART
      - 1 year in other cases

- If <30 years
  - Cytology and colposcopy/biopsy
Should we screen women for anal cancer?

- In the general population, anal cancer is more frequent in women than men but remains rare
  - 1/100,000 in men
  - 2/100,000 in women

- In HIV-positive women

Silverberg M and al. CID 2012

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>HIV-Infected</th>
<th>HIV-Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSM</td>
<td>Other Men</td>
</tr>
<tr>
<td>No.</td>
<td>18 855(^a)</td>
<td>6492(^a)</td>
</tr>
<tr>
<td>Cases</td>
<td>122</td>
<td>14</td>
</tr>
<tr>
<td>Person-years</td>
<td>93 063</td>
<td>30 570</td>
</tr>
<tr>
<td>Median years follow-up (IOR)</td>
<td>4.0 (1.6–7.8)</td>
<td>3.9 (1.6–7.2)</td>
</tr>
<tr>
<td>Incidence rate per 100 000 person-years (95% CI)</td>
<td>131 (109–157)</td>
<td>46 (25–77)</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>80.3 (42.7–151.1)(^d)</td>
<td>26.7 (11.5–61.7)(^d)</td>
</tr>
</tbody>
</table>
There are limitations

➢ Technical:
  • Digital anorectal examination (DARE): no guidelines
  • Anal cytology: poor correlation with the level of dysplasia
  • High resolution anoscopy: is golden standard but costly, timely and few teams are properly trained

➢ Scientific:
  ▪ No randomised study showed a decrease in mortality after anal cancer screening implementation either by DARE/cytology/HRA
  ▪ One randomised study is ongoing NCT01946139 to evaluate the best technique HPV testing/cytology/HRA in women
  ▪ The ANCHOR study (NTC02135419) is designed to determine whether treating AIN2/3 in HIV-infected persons >35 y will prevent anal cancer

Proposal
➢ All HIV-positive women: DARE and routine assessment of anal symptoms
➢ Cytology and HRA in women at higher risk of cancer
  ➢ If CD4 nadir low: < 50-200 lymphocytes CD4/μl
  ➢ If other HPV-related cancer
Preventive Vaccines

External capsid:
L1 protein

Bivalent (BHPV)
Cervarix® GSK:
HPV 16/18 + ASO4
(monophosphoryl lipid A = detoxified derivative of LPS of Salmonella adsorbed on aluminium)

Approval by EMA & FDA:
2007
- Females
- Precancerous lesions in the cervix, vulva or vagina
- Cervical cancer

Quadrivalent (QHPV)
Gardasil® Merck:
HPV 6/11 + 16/18

2006
- Females and males
- Precancerous lesions in the cervix, vulva or vagina and anus
- Cervical and anal cancers
- Genital warts

Ninevalent (NHPV)
Gardasil9® Merck:
HPV 6/11 + 16/18/31/33/45/52/58

2014/15
- Females and males
- Precancerous lesions in the cervix, vulva or vagina and anus
- Genital warts

Non-infectious HPV VLP
Preventive Vaccine in HIV-negative population

- Very efficient against HRHPV vaccinal types of Infection
  - Young women: cervix, vulva/vagina: yes
  - Women 26-45 years: yes
  - Young women: anus, oral: yes
  - Young men: condyloma/perianal: yes
  - Young MSM: HGAIN: yes

- Safe
- Long term protection: immunogenicity up to 10 years
- Recommended by
  - WHO: girls
  - ECDC (2008-2012): girls
  - US, Canada, Australia: girls and boys and MSM up to 26 y
Preventive vaccine in HIV+ patients

**Immunobridging studies**

What about clinical efficacy?
Concerns in HIV patients

• **Cost?**
  - in most European countries, HPV vaccination is recommended for girls 9-13 with catch up program and thus reimbursed 65-100% by the national health authorities
    - 200-375 € for 3 doses

• **How many doses?**
  - Can we give 2 doses before 15 years?
  - Could even one dose be enough?

• **Do we cover all HRHPV genotypes?**

No data in HIV-positive patients!
HPV genotype distribution in HG CIN in HIV positive and negative women

adapted from Clifford G. *AIDS* 2006.
Proportion of women infected with HRHPV genotypes that are included in the different vaccines

<table>
<thead>
<tr>
<th>Prevalence of women of whom all or a part of HRHPV types are covered by</th>
<th>Current HPV vaccines including HRHPV 16/18</th>
<th>Ninevalent HPV vaccine including HRHPV 16/18/31/33/45/52/58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among all women (n=116)</td>
<td>24%</td>
<td>79%</td>
</tr>
<tr>
<td>Among women with abnormal cytology (n=44)</td>
<td>27%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Konopnicki D and al. Accepted in AIDS 2015
Is vaccination indicated in patients with high grade lesions as secondary prophylaxis?

Women (HIV-negative)


• Decreased in recurrent lesions
  - 65% 2 years after treatment of CIN2-3 and vaccination
  - 35% 2 years after treatment of condyloma and vaccination

2.5% had recurrent CIN 2-3 among women vaccinated vs 7.2% in non vaccinated women

How does it work?

• Strong HPV specific cell mediated immune responses in HIV-infected adolescents and young adults similar to HIV-negative

• 46 young adolescents/adults followed up to 28 weeks

Rainone V and al. AIDS 2015
Should we vaccinate HIV-positive patients?

• High burden of disease
• Good immune efficacy and tolerability

The answer should be « Yes »!

• We propose to vaccinate
  – Girls and boys
  – Young women and men up to 26 years
  – When treating high grade lesions
  – Women up to 45 years
Does cART prevent HPV infections or HPV-induced lesions?

- **NO**
  - Design: N
  - Endpoints: Duration of cART
  - Palefsky Cross before <100 anal HPV prev.
  - JAIDS 2001 + after cART + AIN

- **YES**
  - Design: N
  - Endpoints: Duration of cART
  - Heard Longitudinal 168 Regression of CIN
  - AIDS 2002 Better if cART (HR 1.93; 95% IC, 1.14 - 3.29)
  - Fife Longitudinal 146 cervical HPV
  - JAIDS 2009 Prevalence decreased from 62% to 39% (p=.003)
  - Minkoff Longitudinal 286 cervical HPV prev.
  - JID 2010 Incidence + SIL adherence & effecti.
  - Reduction in HPV prevalence (22 to 14%), incidence (5 to 3/100 PV) & SIL prevalence; better clearance of SIL
Cohort of 652 women, 38 years, successfully treated for HIV FU 61 months. Sustained viral suppression reduces the risk of persistent HRHPV. Konopnicki D. *JID*. 

Cohort of 1123 women on cART, FU 66 months. Adler D. *AIDS*. 

Cohort of 750 women. Blitz S. *JID*. Longitudinal study 300 women on cART for 22 months. Zeier M. *AIDS*. 


Use of HAART was associated with: 

- Decrease in incident SIL 
- Increase in regression of SIL 
- Decrease in HRHPV prevalence 
- Increase in regression of SIL 

Every month on cART reduced the risk of any HPV 9% (0.89–0.94) of HPV 16 50% (0.37–0.67) of HPV 18 3.13 times higher chance if 85% adherence and >3 years of cART. 

Factors affecting chance of high-risk HPV any time during study: 

- above 500 copies 31% reduced risk of cervical cancer 0.20 (0.05–0.77) if 85% adherence and >3 years of cART. 

**Thursday 22 Oct 15 PM** 

**Opportunistic infection and tumours** 

**Room Cologne**
...this might mean...

...that patients with HG lesions or at risk (HRHPV+) should be treated by cART whatever the CD4 cell count is...

...prospective randomised studies on this issue would not be ethical as the CD4 lymphocyte count threshold for treating HIV-patients has raised...

So the answer might come from cohort studies after several years
**Conclusion: in HIV-infected women**

- Infection with HPV and HPV-related cancerous lesions are more frequent and severe.

- **Preventive vaccines against HPV are safe and immunogenic: they should be implemented in HIV-infected children and adults.**

- HPV testing for primary cervical screening could become the gold standard in women after 30 years.

- Studies on anal cancer screening and treatment in women are ongoing.

- **cART decreases infection by HRHPV and induced lesions but favourable impact appears after several years.**