Human Papillomavirus (HPV) and HIV co-infection in women and men

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Disclosure

• Travels and congress Grants from Pfizer, BMS and GSK

• No conflicts of interest
Agenda

- HPV and cancer
- HPV and HIV interactions
- The burden of HPV in HIV-infected patients
- Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-infected patients
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THREE-DIMENSIONAL MODEL OF HUMAN PAPILLOMAVIRUS

Major Capsid Protein (L1)

Viral Nucleic Acid (DNA)

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Published in The PRN Notebook, Volume 6, Number 3, September 2001 and The PRN Notebook Onl
Three-dimensional model of HPV created by Louis E. Henderson, Ph.D., Frederick Cancer Resi
HPV-induced cancers

- Cervix
- Anus
- Vagina
- Vulva
- Penis

- Oro-pharyngal

[70% of high-risk HPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68]
Epidemiology of invasive cervical cancer per /100,000 women year (Globocan 2012)

### Estimated Cervical Cancer Incidence Worldwide in 2012

**From Globocan 2012**

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>528,000/year</td>
<td>266,000/year</td>
</tr>
<tr>
<td>Less developed regions</td>
<td>85%</td>
<td>87%</td>
</tr>
<tr>
<td>India</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

![World map showing incidence and mortality rates of cervical cancer](map.png)
Agenda

- HPV and cancer
- **HPV and HIV interactions**
- **The burden of HPV in HIV-infected patients**
- Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-infected patients
HPV and HIV interactions

• HIV increases HPV infection and HPV-induced lesions

➢ Molecular level
  In vitro and ex vivo:
  Adding HIV proteins or cytokines
  • Increases epithelial tight junction disruption
  • Enhances the expression of E6 E7 oncoproteins

➢ Clinical level

Vernon. Virus Res 1993
Tugizov. Virology 2013
Infection by HPV and HPV-induced lesions in the cervix in HIV-positive women

• High risk HPV
  - Prevalence: 43% vs 12%
  - Incidence: 13.4% vs 5% women year

Konopnicki D. JIAS 2013

• Cervical dysplasia
  - Prevalence of abnormal cytology
    - HIV+: 38%
    - HIV-: 16% ¹
  - Incidence of abnormal cytology
    - HIV+: 20%
    - HIV-: 5% after 30 months ²


• After conisation:
  - Normal cytology after conisation: 33% HIV+ vs 66% HIV-
Infection by HPV and HPV-induced lesions in HIV-positive MSM

• HPV Prevalence:
  - all HPV 93% (vs. 64%)
  - HR HPV 74% (vs. 37%)
  - Plateau from young to 50-60 years old

• Prevalence HGAIN
  - 43-52%
  - 25%
  - Risk increases with age
    - 40-49 years OR 3.09
    - >50 OR 4.78
    - Compared to <40 years

• Incidence of HGAIN (HR anuscopy):
  - 8.5-15.4% patients/year
  - vs. 3.3-6% patients/year in HIV-neg MSM

Machalek and al. The lancet oncol. 2012
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.

• **Dysplastic lesions**
  - Prevalence and incidence of dysplastic lesions are higher.
  - Spontaneous regression are less frequent.
  - Recurrence after treatment are more frequent.
### Epidemiology in HIV-positive patients

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

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence per 100,000 person-years</th>
<th>(General Population)</th>
<th>1980-1989 Before ART</th>
<th>1990-1995 ART</th>
<th>1996-2004 Early HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anus (men MSM)</strong> In situ/ Invasive</td>
<td>90/52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anus (men MSW)</strong> In situ/ Invasive</td>
<td>21/14</td>
<td>1.7</td>
<td>18.3</td>
<td>29.5</td>
<td>42.3</td>
</tr>
<tr>
<td><strong>Anus (women)</strong> In situ / Invasive</td>
<td>33/15</td>
<td>0</td>
<td>1.7</td>
<td>5.2</td>
<td>11.2</td>
</tr>
<tr>
<td><strong>Cervix</strong> In situ/ Invasive</td>
<td>9/6</td>
<td>178</td>
<td>449</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td>1.6</td>
<td>0</td>
<td>3.9</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td><strong>Penis</strong> In situ/ Invasive</td>
<td>20/5</td>
<td>1.7</td>
<td>1.7</td>
<td>4.2</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Vagina or Vulva</strong> In situ/ Invasive</td>
<td>27/6</td>
<td>17</td>
<td>54</td>
<td>60</td>
<td>8</td>
</tr>
</tbody>
</table>

Chaturvedi A.  
*J Natl Cancer Inst.* 2009
**HPV and HIV interactions**

- HIV infection increases HPV infection and HPV-induced lesions

- HPV infection favours the acquisition of HIV
HPV increases risk for HIV acquisition: what are the explanations?

- HPV-induced lesions could produce genital epithelium disruption or inflammation, enhanced microcirculation similar to tissue micro trauma?
- HPV clearance is associated with HIV acquisition because of the increased recruitment of cells such as T-lymphocytes in the genital epithelium that are HIV target cells (Averbach S. AIDS 2010; Auvert B. JID 2010).
- HPV clearance was significantly associated with HIV acquisition. Density of dendritic cells in the epithelial foreskin was significantly increased in patients that acquired HIV. 
  
  Tobian A. J Infect Dis. 2013;207:1713-1722
Agenda

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

- Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-infected patients
Condom and circumcision

- **Condoms** confer partial protection in HIV-negative couples both hetero- and homosexual. *What about HIV patients?*
- **Circumcision** decreased the prevalence and incidence of HRHPV in HIV-positive heterosexual men. Although it decreases also the prevalence in female partners when HIV-negative, *data in HIV-positive women and MSM are too scarce to draw similar conclusions.*
Preventive Vaccine

**Quadrivalent (HPV4)**
Gardasil®Merck:
L1 from HPV 6, 11, 16 and 18
Approval for EMA & FDA: 2006
0, 2 and months 6

**Bivalent (HPV2)**
Cervarix®GSK:
L1 from HPV 16 and 18 + ASO4
Approval for EMA & FDA: 2007/9
0, 1 and 6 months
# Vaccine efficacy in HIV-negative patient

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Population</th>
<th>Efficacy against HPV or lesions induced by vaccinal type</th>
<th>Cross protection against non vaccinal type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagina Vulva</td>
<td>Warts+VAIN2+ VIN2+</td>
<td>Naive</td>
<td>100%</td>
<td>Garland S. NEJM 2007.</td>
</tr>
<tr>
<td>Anus Anal HPV in women</td>
<td>18-25 years</td>
<td>84%</td>
<td>HPV2: 62% 49%</td>
<td>Kreimer A. Lancet Oncol 2011</td>
</tr>
<tr>
<td>Anus External lesions (warts + penile, scrotal or perianal), persis. HRHPV HGAIN</td>
<td>Men (15%MSM) 16-26 years</td>
<td>Naive/Not naive</td>
<td>90%/60% 78%</td>
<td>Giuliano A. NEJM 2011</td>
</tr>
<tr>
<td>Palefsky. NEJM 2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Oral HPV16 in women</td>
<td>18-25 years</td>
<td>93%</td>
<td></td>
<td>Herrero. PLoS one 2013</td>
</tr>
</tbody>
</table>
# HPV vaccination

## Recommendation in the general population

- **WHO**
  - Vaccinate girls 9-13

- **ECDC (2008-2012)**
  - Vaccinate girls 9-15
  - Catch up vaccination according to countries guidelines
  - 19/29 countries have introduced the vaccine
  - Coverage 17-84%

- **US**
  - Vaccinate girls 11 to 12 (may start at 9)
  - Catch up vaccination 13 to 26
  - Males 11-12 (may start at 9), Catch up vaccination up to 21-26

### Cost-effectiveness of HPV vaccine

<table>
<thead>
<tr>
<th></th>
<th>Cost-effectiveness of HPV vaccine</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><em>In particular if coverage in female is low</em></td>
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<table>
<thead>
<tr>
<th></th>
<th>Boys Vaccination</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Currently USA, Canada and Australia</td>
</tr>
</tbody>
</table>
Preventive vaccine in HIV+ patients

**Quadrivalent vaccine**  4 studies

- Children
- Females adolescents & adults (up to 45 y)
- MSM median age 44 y
- High CD4 or cART

- **Good Immunogenicity & anamnestic response**
- **Good Safety, no deleterious effect on CD4 nor VL**
- **Cellular immunity:**
  - HPV16 specific CD4+ T cells response was substantially increased from month 2 to 12 in more than 82%

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**Studies on clinical efficacy?**

Levin. *J AIDS*. 2010
Wilkin. *JID* 2010
Weinberg A. *JID* 2012.

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The study of HPV16 was also effectively after 3 and 4 doses.
Unresolved issue in HIV-positive patients

HPV genotype distribution in HG CIN in HIV positive and negative women
adapted from Clifford G. AIDS 2006.

Prevalence of HPV vaccine type in HGAIN in MSM in USA

HPV 2/4v 56.4%
HPV 9-v 89%
16/18/31/33/45/52/58 +6/11

Sahasrabudhe V. JID 2013
Proportion of women infected with HRHPV genotypes that could be covered by 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=126)</td>
<td>27%</td>
<td>77%</td>
</tr>
<tr>
<td>Among women with abnormal cytology (n=48)</td>
<td>28%</td>
<td>82.5%</td>
</tr>
</tbody>
</table>

Konopnicki D.
14th EACS Conference, October 16-19th 2013, Brussels. Poster PE 17/13
Genotype distribution in HIV-positive women in India

- Study in Maharashtra
  - 1109 HIV-infected women
  - In HGCIN according to biopsy

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV16</td>
<td>58.5%</td>
</tr>
<tr>
<td>HPV31</td>
<td>22.6%</td>
</tr>
<tr>
<td>HPV56</td>
<td>13.2%</td>
</tr>
<tr>
<td>HPV18, HPV68a</td>
<td>11.3%</td>
</tr>
</tbody>
</table>

Joshi S. Vaccine 2014
• A study of HPV Genotypes among HIV infected women from Andhra pradesh
• Surya Rao Kutikuppala
• Session 12 Malignancy and HIV
• Saturday 22\textsuperscript{nd} march
• 15h20
The impact of HPV vaccination on HPV infection and on HIV transmission

HPV-infection prevalence in the cervix and invasive cervical cancer incidence according to WHO HIV seroprevalence distribution in 2010

HPV prevalence in all women
HPV prevalence in HIV-positive women
ICC incidence in all women / 100.000 women-year

Bruni L. *JID* 2010
Clifford G. *AIDS* 2006
Globocan 2008
Tabrizi N. *JID* 2012. Mesher D. *Vaccine* 2013

**HPV 16/18**
17% → 6%

**HPV 16/18/6/11**
28.7% → 6.7%

Immunodepression
• Induced lesions
• Shedding

Susceptibility

HIV
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
- Colposcopy + biopsy
- LG CIN
  - Pap-smear after 6 months
  - Colposcopy + biopsy after 1 year
  - HG CIN
  - Conisation

- Pap-smear after 6 months
- Colposcopy + biopsy after 1 year
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
- HPV pos
- Check after 1 year
- Check after 6 months

Colposcopy + biopsy
- LG CIN
- HG CIN

Pap-smear after 6 months
- Conisation
- Colposcopy + biopsy after 1 year

Normal
Cervical screening in developed countries

**Could this be applied to HIV-positive women?**

- Under 30 years HPV prevalence is too high
- 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.

Cervical screening in limited resource setting: HPV testing

Screen-and-treat approach

South Africa. Excluded macroscopic lesions (6%).

Kuhn and al. AIDS 2010
Screen and treat approach

• Cervical Cancer Prevention in HIV-infected women using the « see and treat » approach in Botswana.
  Ramogola-Masire D. J Acqui Immune Def Syndr 2012

• Screening of cervical neoplasia in HIV-infected women in India.
  Joshi S. AIDS 2013.
• Observational Study of a large cohort of HIV-infected women screened for cervical cancer
• Vinay Kulkarni
• Session 12 Malignancy and HIV
• Saturday 22\textsuperscript{nd} march
• 15h20
Anal screening in HIV patients should be implemented... but questions remain for HIV-patients: 

Who?

- MSM: Incidence cancer 80/100,000 persons-year

- Women: Incidence cancer 16/100,000 persons-year

Should Anal screening be implemented for all women?

Natural history of AIN could differ from CIN

Nadir CD4<50

CD4<200/µL associated with abnormal cytology

(AOR 2.4, p=.001 RR 4.87, p=.004) Conley. JID 2010.

Anal screening in HIV patients

Cytology

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

- ASC-US
  - Anoscopy with biopsy
    - No lesion seen

- LSIL
  - AIN I
    - Follow-up in 6 months or treat if minimal potential for morbidity

- HSIL (or ASC-H)
  - AIN II or III
    - Treat

• Anal cancer in HIV infected individuals
• Sheela Sawant
• Session 12 Malignancy and HIV
• Saturday 22\textsuperscript{nd} march
• 15h20
Does cART prevent HPV infections or HPV-induced lesions?

- **NO**
  - Design: Palefsky Cross S before <100 anal HPV prev. 6 months
  - JAIDS 2001 + after cART + AIN

- **YES**
  - Design: Heard Longitudinal 168 Regression of CIN 12 months
  - AIDS 2002 Better if cART (HR 1.93; 95% IC, 1.14 - 3.29)
  - Fife Longitudinal 146 cervical HPV 24 months
  - JAIDS 2009 Prevalence decreased from 62% to 39% (p=.003)
  - Minkoff Longitudinal 286 cervical HPV prev. 30 months
  - 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
...more recently

Cohort of 652 women, 38 years, successfully treated for HIV, FU 61 months
Sustained viral suppression and higher CD4 T cell reduces the risk of persistent HRHPV
Konopnicki D.  *JID* 2013
Risk of Anal Cancer in HIV-Infected and HIV-Uninfected Individuals in North America

- 13 cohorts from North America 1996-2007
- 34,000 HIV-infected patients
  - 55% MSM, mostly caucasian
  - 19% heterosexual Men, mostly Black and
  - 26% Women, heterosexual HIV transmission
- 114260 HIV-negative patients
Reference is HIV-uninfected men

From Silverberg M and al. CID 2012:54 (1 april)
Treatment of high grade lesions

- **Ablative techniques (no diagnostic)**
  - Cryotherapy (CO2)
  - Surgery: Laser, electrosurgery, electrocautery, infrared coagulation

- **Excisional procedures** (both diagnostic and therapeutic)
  - Loop excision
  - Conisation
  - Hysterectomy

- **Topical treatment**
  - Trichloroacetic acid: efficient in low grade, limited diseases
  - Imiquimod
  - 5FU
  - Cidofovir

- **Therapeutic vaccine**

  *Indication: perianal or vulvar high grade lesions >3 cm²*

  Pilot study in HIV+ patients by Stier E. AIDS 2013

  Cidofovir 1% cream
  6 cycles of 2 weeks:
  Once/day for 6-8 h from day 1 to 5, then 9 days off

  51% had complete or partial response
Therapeutic vaccine

**Vulvar cancer**

Kenter. *NEJM* 2009

- 30 HIV-negative women with HPV-16 VIN3
- 3-4 injections (2.8 ml) mix of long peptide from HPV-16 E6 and E7
- Swelling 100% Fever 64%
- At months 12, 15/19 had clinical response (CR=9), +1 carcinoma
- At months 24, the 9 CR maintained, +1 carcinoma in situ

**Anal cancer**

Anderson. *JAIDS* 2009

- Randomised, double-blind, placebo- controlled: 35 MSM HIV+ (CD4=627)
- 3 doses 0.5 ml at Day 1, 14/30, 70/90 HPV-16 E6E7
- Safety: moderate to severe short term reaction 5/35 had transient VL
- Strong and durable Ab response. Moderate IFN G response during 6 months
- Not powered to detect clinical efficacy
Conclusion: in HIV-infected patients (1)

- Infection with HPV and HPV-related cancerous lesions are more frequent and severe in HIV-infected patients.

- HPV infection (and in particular its clearance) favours the acquisition of HIV.

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

- Scaling up the HPV vaccine could decrease HIV transmission in regions with high HPV prevalence.
Conclusion: in HIV-infected patients (2)

• HPV testing for primary cervical screening could become the gold standard in both developed and in developing countries in women after 30 years.

• Anal screening should be implemented for MSM... and a subset of women?

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

• In addition to specific therapy, cART should be started in patients with ano-genital dysplasia at least of high grade.