HIV, cancer, HPV & STI’s

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Brussels
HIV and cancer

• AIDS-defining malignancies:
  – Kaposi’s sarcoma
  – Non Hodgkin lymphoma 1985
  – Cervical cancer 1993

• Non AIDS-defining malignancies (NADM) is increasing
  • Linked with virus HPV (Anal), HBV and HCV (Liver), EBV (HL)
  • Linked with previous immunodeficiency and other factors
Before introduction of HAART, ADCs common, including Kaposi’s sarcoma, NHL, and invasive cervical carcinoma.

Rate of ADCs significantly increased from early to late pre-HAART era and then significantly decreased following introduction of HAART.

Rates of nADCs stable during pre-HAART eras and then significantly increased following introduction of HAART.
AIDS-Defining Cancer

\[ \text{SIR} = \frac{\text{Nb cases of cancer in the HIV population}}{\text{Expected nb of cases in the general population, calculated with local cancer registry incidence}} \]
Cancer Incidence in AIDS Patients

- Study of cancer risk in AIDS patients from 1980-2006 (N=372,364)
- Predominantly male (79%), non-hispanic black (42%), MSM (42%)
- Median age of 36 years at the onset of AIDS

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SIR=Standardized Incidence Ratios
Cancer-related causes of death.

<table>
<thead>
<tr>
<th>Reported deaths</th>
<th>Mortalité 2000</th>
<th>Mortalité 2005</th>
<th>Mortalité 2010</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer-related causes of death, n (%)</td>
<td>964</td>
<td>1042</td>
<td>728</td>
<td></td>
</tr>
<tr>
<td>AIDS-related, n (%)</td>
<td>269 (27.9%)</td>
<td>344 (33.0%)</td>
<td>262 (36.0%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>149 (15.5%)</td>
<td>134 (12.9%)</td>
<td>68 (9.3%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>105 (10.9%)</td>
<td>103 (9.9%)</td>
<td>53 (7.3%)</td>
<td>0.129</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>4 (0.4%)</td>
<td>6 (0.6%)</td>
<td>4 (0.5%)</td>
<td>0.848</td>
</tr>
<tr>
<td>Hepatitis-related, n (%)</td>
<td>17 (1.8%)</td>
<td>37 (3.6%)</td>
<td>31 (4.3%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>8 (0.8%)</td>
<td>27 (2.6%)</td>
<td>19 (2.6%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>7 (0.7%)</td>
<td>6 (0.6%)</td>
<td>10 (1.4%)</td>
<td>0.279</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>2 (0.2%)</td>
<td>4 (0.4%)</td>
<td>2 (0.3%)</td>
<td>0.732</td>
</tr>
<tr>
<td>Non AIDS/non hepatitis related, n (%)</td>
<td>103 (10.7%)</td>
<td>173 (16.6%)</td>
<td>163 (22.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory</td>
<td>50 (5.2%)</td>
<td>65 (6.2%)</td>
<td>78 (10.7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Lung</td>
<td>44 (4.6%)</td>
<td>53 (5.1%)</td>
<td>61 (8.4%)</td>
<td>0.040</td>
</tr>
<tr>
<td>Ear, nose and throat</td>
<td>6 (0.6%)</td>
<td>12 (1.2%)</td>
<td>17 (2.3%)</td>
<td>0.056</td>
</tr>
<tr>
<td>Digestive</td>
<td>6 (0.6%)</td>
<td>13 (1.2%)</td>
<td>10 (1.4%)</td>
<td>0.342</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3 (0.3%)</td>
<td>11 (1.1%)</td>
<td>7 (1.0%)</td>
<td>0.282</td>
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<tr>
<td>Anal</td>
<td>6 (0.6%)</td>
<td>11 (1.1%)</td>
<td>13 (1.8%)</td>
<td>0.073</td>
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<tr>
<td>Skin</td>
<td>2 (0.2%)</td>
<td>10 (1.0%)</td>
<td>3 (0.4%)</td>
<td>0.065</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>12 (1.2%)</td>
<td>9 (0.9%)</td>
<td>8 (1.1%)</td>
<td>0.473</td>
</tr>
<tr>
<td>Other hemopathies</td>
<td>5 (0.5%)</td>
<td>8 (0.8%)</td>
<td>7 (1.0%)</td>
<td>0.602</td>
</tr>
<tr>
<td>Breast</td>
<td>3 (0.3%)</td>
<td>7 (0.7%)</td>
<td>5 (0.7%)</td>
<td>0.647</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>4 (0.4%)</td>
<td>6 (0.6%)</td>
<td>2 (0.3%)</td>
<td>0.530</td>
</tr>
<tr>
<td>Other and unknown</td>
<td>12 (1.2%)</td>
<td>33 (3.2%)</td>
<td>27 (3.7%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Multiple</td>
<td>-</td>
<td>-</td>
<td>3 (0.4%)</td>
<td>-</td>
</tr>
</tbody>
</table>


*a* Comparisons between 2000, 2005 and 2010 adjusted on age and gender

*b* Including 3 patients with both non-Hodgkin lymphoma and Kaposi sarcoma

*c* See Appendix for details

*d* Multiple: anus + prostate, anus + lung, lung + breast
Location of cancers (N = 268) among HIV-infected adults with underlying cause of death being cancer (N = 262), Mortalité 2010 survey, France.
Increased rates of nADCs. Why?

- Increasing survival of patients with HIV might be associated with an increase of traditional cancer risk
- Aging of the HIV population
- Long-term toxicity of ART?
Increased rates of nADCs. Why?

Other possible explanations:

• Confounding by shared lifestyle cancer risk factors

  Tobacco use
  – MSM have nearly double the rate of tobacco use compared to all U.S. men: 48% vs 29% (Stall 1999)

  – A role of HIV through its effect on immune deficiency

Importance:
  – If immune deficiency is responsible, then reversing immune deficiency might decrease cancer risk
Characteristics of cancer immune control

- CD4 cell count
- CTL function
- NK
- Immune memory Central/effector memory
- Level of immune activation:
  - PD-1, IL-10, Treg
- Immune system on pre-cancerous lesions
Cancers in HIV and transplant patients

• The range of cancers occurring at increased rates is strikingly similar in the two groups

• Mostly those known or suspected to be caused by infective agents

• Impact of immunodeficiency on these cancers
Incidence of first NADM (with 95% CI) stratified by different indicators of immunosuppression

- Latest CD4 (cells/mm$^3$)
- Lagged CD4 (cells/mm$^3$), 6 months
- Nadir CD4 (cells/mm$^3$)
- Time-averaged CD4 (cells/mm$^3$)
Incidence of first NADM (with 95% CI) stratified by duration of immunosuppression (years)

RR /year: 1.05 (1.04, 1.06), p=0.0001

RR /year: 1.05 (1.03, 1.07), p=0.0001
Incidence of first NADM (with 95% CI) stratified by indicators of viraemia

Latest HIV RNA

AUC for HIV RNA

RR /log higher (log 10 copies/ml): 1.05 (0.99, 1.13), p=0.13

RR /unit: 1.04 (1.00, 1.09), p=0.07
NADCs in HIV+ Patients compared to Cancer in HIV (-) Patients

- Occur at a younger age (?)
- Atypical pathology, higher tumor grade
- Diagnosed at more advanced stage
- More aggressive disease course
- Poorer outcomes
- Higher rate of relapse
Let’s concentrate on Non AIDS-Defining Cancers
Hodgkin disease
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HIV and Hodgkin’s Lymphoma

- Due to co-infection with EBV
  - Co-infection rates 75 to 100%, vs 20 to 50% in HIV- HL
- More aggressive disease
  - Histology: mixed cellularity, lymphocyte depleted
  - B symptoms present (fevers, sweats, weight loss)
  - Extra-nodal disease common (75 to 90%)
  - Bone marrow involvement common (40 to 50%)
- Effect of HAART therapy on risk unclear, contradictory

Hepatocellular carcinoma
Cancer Incidence in AIDS Patients

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SIR=Standardized Incidence Ratios
HIV and Liver Cancer

- Incidence rate 7 times higher in HIV +
- Due to Hepatitis B and C co-infection
- Lower risk in HIV patients on HAART (Only NADC)
- Higher risk of extrahepatic metastases, poorer outcome
- Treatment with transplantation complicated

Lung cancer
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Excess of risk of lung cancer in HIV

- Hypotheses for causal factors...
  - increased frequency of smoking in HIV population, but intensity and duration not different
  - HIV status seems probable, but the mechanisms remain unknown:
    - degree of immune deficiency
    - duration of immune deficiency
    - oncogenic role of HIV *per se*
    - other oncogenic virus
    - role of HAART
Lung Cancer

- Most frequent NADC in HAART era
- Incidence 2-4 fold higher than general population
  - SIRS between 2 and 3 and stable over time
- Diagnosed at younger age with advanced disease and primarily in smokers
- Adenocarcinoma is most frequent sub-type
- No clear screening strategy
- No argument to treat differently than non-HIV infected patients
Breast cancer
Breast cancer

- No higher incidence in HIV-positive women

- There might even be a lower incidence:
  - Significant decrease was recorded in Tanzania following HIV epidemics. Amir. J Natl Med Assoc 2000
  - Significant decrease in relative risk (observed cases/expected cases based incidence in general population). Frisch. JAMA 2001
  - Goedert Br J Cancer 2006
Why breast cancer could be less frequent in HIV women?

• Reduced incidence is also found in other immunosuppressed patients (suggesting that physiological immune response is a facilitating factor in breast carcinogenesis)

• Hormone production is reduced in HIV: oestradiol or testosterone

• CXCR4-tropic HIV is protective against breast cancer because

• Ritonavir has been studied in preclinical trials for its activity against breast cancer growth
## Cancer screening – EACS

<table>
<thead>
<tr>
<th>Problem</th>
<th>Patients</th>
<th>Procedure</th>
<th>Evidence of benefits</th>
<th>Screening interval</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Women 50–70 yrs</td>
<td>Mammography</td>
<td>↓breast cancer mortality</td>
<td>1–3 years</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Sexually active women</td>
<td>Papanicolau test, HPV DNA test</td>
<td>↓cervical cancer mortality</td>
<td>1–3 years</td>
<td>Target age group should include at least the age range 30 to 59 years. Longer screening interval if prior screening tests repeatedly negative</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Persons 50–75 yrs</td>
<td>Fecal Occult Blood test</td>
<td>↓colorectal cancer mortality</td>
<td>1–3 years</td>
<td>Benefit is marginal</td>
</tr>
</tbody>
</table>
HAART and chemotherapy

• Many patients will receive HAART and chemotherapy concurrently with high likelihood of drug interactions and overlapping toxicities
• Protease inhibitors and non-nucleoside reverse transcriptase inhibitors are substrates and potent inhibitors or inducers of cytochrome P450 system (CYP)
  – Many anti-neoplastic drugs also metabolized by CYP system leading to either drug accumulation and possible toxicity or decreased efficacy
## Chemotherapy and HAART

<table>
<thead>
<tr>
<th>Enzyme/Transporter</th>
<th>HAART Inhibitors</th>
<th>HAART Inducers</th>
<th>Chemotherapy Substrates</th>
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</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>delavirdine, efavirenz, ritonavir, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir</td>
<td>nevirapine, efavirenz</td>
<td>paclitaxel, docetaxel, erlotinib, sunitinib, sorafenib, etoposide, vincristine, vinblastine, vinorelbine, cyclophosphamide</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>efavirenz, ritonavir</td>
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<td>cyclophosphamide</td>
</tr>
<tr>
<td>CYP2C19</td>
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<td>cyclophosphamide, ifosfamide, thalidomide</td>
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<tr>
<td>CYP2D6</td>
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<td>tamoxifen</td>
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<tr>
<td>CYP2B6</td>
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<td>nevirapine</td>
<td>cyclophosphamide, ifosfamide</td>
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<tr>
<td>CYP2E1</td>
<td>ritonavir</td>
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<td>etoposide, dacarbazine</td>
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<tr>
<td>UGT1A1</td>
<td>atazanavir</td>
<td></td>
<td>irinotecan</td>
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</table>
## Drug Transporters

<table>
<thead>
<tr>
<th>Drugs</th>
<th>ABCB1</th>
<th>ABCC1</th>
<th>ABCG2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Didanosine (DDI)</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Stavudine (D4T)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Zalcitabine (ddC)</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
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<td>+</td>
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</tr>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine disoproxil fumarate</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
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</tr>
<tr>
<td>Nevirapine</td>
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</tr>
<tr>
<td>Efavirenz</td>
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<tr>
<td>PI</td>
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<tbody>
<tr>
<td>Actinomycin D</td>
<td>Etoposide</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Teniposide</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Daunorubicin</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Epirubicin</td>
<td>Topotecan</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Melphalan</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Vincristine</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>Vinblastine</td>
<td>Gefitinib</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Vincristine</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>Etoposide</td>
<td></td>
</tr>
</tbody>
</table>


4, ++, or +++: weak, moderate, or strong substrate/inhibitor. NT: None-toxic, could not be determined.
HPV and cancer in HIV patients
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
Persistent Infection

5-10% If HIV negative
20-30% If HIV positive
# Cervical Intraepithelial Neoplasia

**CIN I (and Warts):**
Mild dysplasia, lower one-third of epithelium
The full complement of HPV DNA and proteins (Early and Late) are produced. Infectious virus is produced in the mature squamous cell layer.

**CIN 2:**
Moderate dysplasia, lower two-thirds of epithelium
More extensive production of E6 and E7 proteins and less extensive production of viral DNA and late proteins than CIN 1.

**CIN 3:**
Severe dysplasia, total involvement of epithelium
Very high level of production of E6 and E7, and little production of late proteins or viral DNA.

**LG-SIL Squamous Intraepithelial Lesions**

**HG- SIL**

**CYTOLOGY**
(Smear)

**HISTOLOGY**
(BIOPSY)
HPV-induced cancers

- Cervix
- Anus
- Vagina
- Vulva
- Penis
- Oro-pharyngal

Low risk HPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

High risk HPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

70%
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

Vernon. Virus Res 1993
Tugizov. Virology 2013

➢ Clinical level
Infection by HPV and HPV-induced lesions in the cervix in HIV-positive women

- High risk HPV
  - **HIV+** vs. **HIV-**
    - Prevalence: 43% vs. 12%
    - Incidence: 13.4% vs. 5% women year

- Cervical dysplasia
  - Prevalence of abnormal cytology: 38% vs. 16% ¹
  - Prevalence in Belgium
    - All: 28% ² vs. 5.9%
    - HSIL: 3% ² vs. 1.2%
  - Incidence of abnormal cytology: 20% vs. 5% after 30 months ³
  - Incidence in Belgium
    - All: 6% women year ²
    - HSIL: 1.4% women year

- After conisation:
  - Normal cytology after conisation: 33% vs. 66% ¹⁷

² Konopnicki D. PhD June 2014
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.

- **Cancer**
  - Incidence 6-10 times higher for the cervix
  - Incidence 40-90 times higher for the anus
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

Normal

Pap-smear after 6 months

Colposcopy + biopsy after 1 year

Conisation
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.

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
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%
  - In Belgium 25% (Libois A. EACS 2013)
  - 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
Anal screening in HIV patients should be implemented... *but questions remain for HIV-patients:*

- **Who?**
  - **MSM:** Incidence cancer 80/100,000 persons-year
  - Salit. AIDS 2010 22% (2001-2005)
  - Palefsky. AIDS 2005

- **Women:** Incidence cancer 16/100,000 persons-year
  - Prevalence of ≥AIN2: 9% (2001-2006)
  - Hessol. AIDS 2009

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
  - LSIL
    - Anoscopy with biopsy
      - No lesion seen
        - Follow-up in 6 months or treat if minimal potential for morbidity
      - AIN I
        - AIN II or III
          - Treat
  - HSIL (or ASC-H)
Does cART prevent HPV infections or HPV-induced lesions?

- **NO**
  - **Endpoints:** Duration of cART
  - **Design:** Cross-S before <100 anal HPV prev. 6 months
  - **Publication:** JAIDS 2001

- **YES**
  - **Endpoints:** Duration of cART
  - **Design:** Longitudinal
  - **Publication:** JAIDS 2009
    - Prevalence decreased from 62% to 39% (p=.003)
  - **Publication:** AIDS 2002
    - Better if cART (HR 1.93; 95% IC, 1.14-3.29)

Additional studies:

- **Publication:** BMC Inf Dis 2010
  - **Design:** Longitudinal
  - **Endpoints:** Regression of CIN
  - **Publication:** AIDS 2002
    - Better clearance of SIL
  - **Publication:** JAIDS 2009
    - Incidence decreased from 5 to 3/100 PV
  - **Publication:** JID 2010
    - Adherence & effect
    - Reduction in HPV prevalence (22 to 14%), incidence (5 to 3/100 PV) & SIL prevalence
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 and of cytological abnormalities

Konopnicki D. JID 2013
What about HPV prevention?
Condoms confer partial protection in HIV-negative couples both hetero- and homosexual. What about HIV patients?

Circumcision decreases 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.
**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
Preventive vaccine in HIV+ patients

**Quadrivalent vaccine**

4 studies

- **Studies on clinical efficacy?**

  Phase IV 2010-2015:
  Thailand, Brazil, USA

  Gardasil vs Cervarix
  in women 15-25 years

  ongoing

**Bivalent vaccine**

- **Good Immunogenicity**
- **Good Safety, no deleterious effect on CD4 nor VL**
- **Cellular immunity:** HPV16/18 specific CD4+T cells response was substantially increased from month 2 to 12 in more than 82%

Levin. *J AIDS.* 2010
Wilkin. *JID* 2010
Weinberg A. *JID* 2012: Denny L. *Vaccine.* 2013

Studies on clinical efficacy in:”

- Phase IV 2010-2015:
  - Thailand
  - Brazil
  - USA

Gardasil vs Cervarix in women 15-25 years

ongoing
...an 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
Ninevalent vaccine

• Gardasil 9® Merck
  – 6, 11
  – 16, 18
  – 31, 33, 45, 52, 58

• Study phase III comparing Gardasil9 to Gardasil
  – N= 14,000 females 16-26 years
  – Efficacy for prevention of CIN2+, VIN2+ or VAN2+ (induced by HPV31/33/45/52/58) : 97%

• Safety similar

• Approved by FDA in Dec 2014 and EMA in March 2015

• 13$ more per dose: cost effective
Is vaccination indicated in patients with high grade lesions as secondary prophylaxis?

Women (HIV-negative)

- **2 randomised studies:** Joura E. *BMJ* 2012. Woo Dae Kang. *Gynecol Oncol* 2013
- Decreased in recurrent lesions
  1. - 65% 2 years after treatment of CIN2-3 and vaccination
  - 35% 2 years after treatment of condyloma and vaccination
  2. 2.5% had recurrent CIN 2-3 among women vaccinated **vs 7.2%** in non vaccinated women

MSM (HIV-negative)

- **2 retrospective studies:** Swedish K. *CID* 2012 & *PLOS ONE* 2014
- Limitations ++ in methodology
- Decrease in recurrence in HGAIN or anal condyloma after treatment and vaccination
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
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.
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.

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

- Therapeutic vaccines are in development
Few words on other sexually transmitted diseases in HIV patients
1. STI’s are HIV indicator diseases
STI prevalences were stable:

8% for Syphilis, 4,8% for Chlamydia, 2,8% for Gonorrhea, 0,8% for Hepatitis C.
# Results – HIV diagnoses per Indicator Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>HIV test</th>
<th>HIV +</th>
<th>Prevalence (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3588</td>
<td>66</td>
<td>1.84 (1.42-2.34)</td>
</tr>
<tr>
<td>STI</td>
<td>764</td>
<td>31</td>
<td>4.06 (2.78-5.71)</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>344</td>
<td>1</td>
<td>0.29 (0.01-1.61)</td>
</tr>
<tr>
<td>Cervical or anal dysplasia</td>
<td>542</td>
<td>2</td>
<td>0.37 (0.04-1.32)</td>
</tr>
<tr>
<td>Herpes Zoster &lt;65yo</td>
<td>207</td>
<td>6</td>
<td>2.89 (1.07-6.21)</td>
</tr>
<tr>
<td>Hepatitis B/C</td>
<td>1099</td>
<td>4</td>
<td>0.36 (0.10-0.93)</td>
</tr>
<tr>
<td>On-going mononucleosis-like illness</td>
<td>441</td>
<td>17</td>
<td>3.85 (2.26-6.10)</td>
</tr>
<tr>
<td>Leuko/thrombocytopenia</td>
<td>94</td>
<td>3</td>
<td>3.19 (0.66-9.04)</td>
</tr>
<tr>
<td>Seborrheic dermatitis/exanthema</td>
<td>97</td>
<td>2</td>
<td>2.06 (0.25-7.24)</td>
</tr>
</tbody>
</table>
## HIV in Europe: Brussels data

HIV prevalence for each of the diseases tested with 95% CI, using the exact binomial method

<table>
<thead>
<tr>
<th>Total indicator disease</th>
<th>N° enrolled</th>
<th>N° test HIV positive</th>
<th>Prevalence (95%CI)</th>
<th>CD4 median</th>
<th>VL (log) median</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total indicator disease</strong></td>
<td>3588</td>
<td>66</td>
<td>1.84 (1.42-2.34)</td>
<td>400</td>
<td>4.79</td>
</tr>
<tr>
<td><strong>A. Sexually transmitted disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>764</td>
<td>31</td>
<td>4.06 (2.78-5.71)</td>
<td>457</td>
<td>4.86</td>
</tr>
<tr>
<td>Female</td>
<td>538</td>
<td>29</td>
<td>5.39%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Gonorrhoea</td>
<td>74</td>
<td>3</td>
<td>4.05 (0.85-5.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Syphilis</td>
<td>80</td>
<td>8</td>
<td>10.00 (4.41-18.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ulcer</td>
<td>73</td>
<td>1</td>
<td>1.37 (0.03-7.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Chlamydia</td>
<td>176</td>
<td>5</td>
<td>2.84 (0.09-6.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Unspecified</td>
<td>373</td>
<td>16</td>
<td>4.29 (2.47-6.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>B. Malignant lymphoma</strong></td>
<td>344</td>
<td>1</td>
<td>0.29 (0.006-1.61)</td>
<td>unk</td>
<td>unk</td>
</tr>
<tr>
<td><strong>C. Cervical or anal dysplasia or cancer</strong></td>
<td>542</td>
<td>2</td>
<td>0.37 (0.04-1.32)</td>
<td>308</td>
<td>5.06</td>
</tr>
<tr>
<td>- Cervical cancer/dysplasia</td>
<td>460</td>
<td>0</td>
<td>0.00 (0.00-0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anal cancer/dysplasia</td>
<td>69</td>
<td>2</td>
<td>2.90 (0.35-10.1)</td>
<td>308</td>
<td>5.06</td>
</tr>
<tr>
<td>- Unspecified (female only)</td>
<td>13</td>
<td>0</td>
<td>0.00 (0.00-24.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>D. Herpes zoster</strong></td>
<td>207</td>
<td>6</td>
<td>2.89 (1.07-6.21)</td>
<td>198</td>
<td>3.76</td>
</tr>
</tbody>
</table>
2. Higher risk of neurosyphilis in HIV patients: consider LP!
3. Syphilis, Chlamydia, Gono, HCV, HBV and HPV are the most prevalent but do not forget:

- Trichomonas vaginalis
- Gardnerella vaginalis
- Mycoplasma genitalium
- and many others...