HIV-positive women and cancer

Deborah Konopnicki
Saint-Pierre University Hospital
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
HIV-positive women and cancer

• Epidemiology
  – ADM and NADM
  – Compared to HIV-negative women
  – Compared to HIV-positive men

• Impact
  – On outcome and mortality
  – Prevention, screening, care

• Focus on breast, HPV-induced cancers
AIDS-Defining Cancer

SIR = Standardised Incidence Ratio

\[
\text{SIR} = \frac{\text{Nb cases of cancer in the HIV population}}{\text{Expected nb of cases in the general population, calculated with local cancer registry incidence}}
\]
OI and cancer incidence/100 patients-years in Saint-Pierre Cohort

Graph showing the incidence of various opportunistic infections and cancer types from 1985 to 2010, including:
- Candidiasis
- Cryptococcosis
- Cytomegalovirus
- Kaposi Sarcoma
- Leuko encephalitis
- Lymphoma
- Mycobacterium avium complex
- PCP
- Toxoplasmosis
- Tuberculosis


**SIR**

<table>
<thead>
<tr>
<th></th>
<th>1990-95</th>
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<td>CC</td>
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</table>
Non AIDS-Defining Cancer
HIV-positive women and NADM

- Incidence of Non AIDS-defining malignancies (NADM) is increasing
  - Linked with aging
  - Linked with virus HPV, HBV and HCV, EBV
  - SIR X 2-3 HIV-negative patients

- Impact on mortality is important
  - NADM have become a major cause of death
Change in percentage of patients >50 years of age among new HIV cases in Europe

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;20 ans</th>
<th>20-24</th>
<th>25-29</th>
<th>30-34</th>
<th>35-39</th>
<th>40-44</th>
<th>45-49</th>
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<td>0</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

**Saint-Pierre Cohort: women age distribution**

- >=60 ans
- 50-59
- 45-49
- 40-44
- 35-39
- 30-34
- 25-29
- 20-24
- <20 ans
Aging and (non-HIV-associated) co-morbidity in HIV-positive persons: The Swiss HIV Cohort Study (SHCS)

- 8138 HIV positive patients (29.4% women)
- Non-HIV co-morbidities, particularly diabetes mellitus, cardiovascular disease, non-AIDS-defining malignancies and osteoporosis, become increasingly important in HIV care, and are frequently age-related
HIV and Fatal Malignancies

D:A:D

- 21 countries Europe, USA and Australia
  - 23,447 HIV+ patients
  - 104,691 person-years of F/U
  - 25% women
- Fatal non-ADM have become more common than ADM
- Incidence of both non-ADM and ADM increases with lower CD4+ cell count but is not affected by HIV RNA

France 2005

- 34% of deaths are cancer related
- 61% of cancers are NADM

Bonnet. *Clin Infect Dis* 2009

Increase in non-AIDS mortality in women: WHIS (n=2792)

- Non-AIDS: Miscellaneous
- Non-AIDS: Overdose/Trauma
- Non-AIDS: Cancer
- Non-AIDS: Liver
- Non-AIDS: Heart
- AIDS

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<th>Year</th>
<th>N</th>
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<th>Indeterminate</th>
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<td>2001–2002</td>
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<tr>
<td>2003–2004</td>
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<td>8</td>
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</tbody>
</table>

SMR: 26
Death rate: 8
2.6/100 person-years

French. JAIDS 2009
Is mortality due to cancer increased in women?

- Mortality after ADM and NADM
  - Cohort 23,000 persons (25% female)
  - Death from cancer (13% female)
  - Being a female vs. a male did not influence cancer mortality

- Mortality after cancer diagnosis
  - Cohort 20,677 persons followed since 1995 across USA
  - Among patients who developed cancer 14% were women (14% survivors=14% deaths)

Achenbach and al. *AIDS* 2011

D:A:D. *AIDS* 2008
Characteristics of non-AIDS defining malignancies in the HAART era: a clinico-epidemiological study

N. Dauby, S. De Wit, M. Delforge, C. Necsoi, N. Clumeck

Journal of AIDS Society 2011

From January 1st 2002 to March 31st 2009:

3126 patients (43% female, n=1344)

12746 patients years of follow up

45 cases of NADM diagnosed (33% female)

Incidence: 3.54 per 1000 patient years
(95% IC 2.22 - 4.86)
## Saint-Pierre Cohort: NADM SIR

### Reference: Belgian Cancer Registry 2005

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>5</td>
<td>5.58</td>
<td>0.90</td>
<td>0.29</td>
<td>2.09</td>
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<tr>
<td>Liver</td>
<td>4</td>
<td>0.38</td>
<td>10.64</td>
<td>2.86</td>
<td>27.23</td>
</tr>
<tr>
<td>Prostate</td>
<td>4</td>
<td>9.17</td>
<td>0.44</td>
<td>0.12</td>
<td>1.12</td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
<td>9.61</td>
<td>0.31</td>
<td>0.06</td>
<td>0.91</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>6</td>
<td>0.34</td>
<td>17.76</td>
<td>6.49</td>
<td>38.67</td>
</tr>
<tr>
<td>Anus/Rectum</td>
<td>6</td>
<td>0.13</td>
<td>46.01</td>
<td>16.80</td>
<td>100.16</td>
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<td>4</td>
<td>1.14</td>
<td>3.52</td>
<td>0.95</td>
<td>9.02</td>
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<tr>
<td><strong>Others (&lt;3)</strong></td>
<td><strong>13</strong></td>
<td></td>
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</tr>
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</table>

Significantly increased incidence of:
   • Hodgkin lymphoma
   • Anal cancer
   • Liver cancer

NADM were associated with
   - higher age
   - lower nadir CD4 count
NADM diagnosis was independently associated with higher mortality (hazard-ratio 4.00; 95% CI 2.36-6.78)

N. Dauby, S. De Wit, M. Delforge, C. Necsoi, N. Clumeck
Journal of AIDS Society 2011
14 vs 32 months; $p = .037$ (Logrank test)
Why mortality could be increased in women?

- **USA**
  - Women have less access to HAART, less decrease in AIDS related mortality
  - Depressive symptoms and history of sex-abuse
  - Unemployment
  - IVDU

- **St-Pierre cohort (n=129)**
  - Women from are from African origin
  - Higher vulnerability
  - Socio economic precarity: 74% are living with less than 1000 euros per months
  - Majority are widows raising children
  - 15% of children are HIV-infected
  - Psychological distress
  - Poor treatment adherence

French. *JAIDS* 2009

O’Doherty. Poster E19.9/2. EACS Dublin 2005
• **Is the epidemiology of cancer different in HIV-positive women?**
  
  – Compared to HIV-negative women
  – Compared to HIV-positive men
HIV-positive patients 1981-2007
1. Lung
2. Hodgkin
3. Anus
4. Colo-rectum
5. Liver

Meta-analysis of 4797 NADM among 625,716 patients
Shiels J Acquir Immune Def Syndr 2009

HIV-positive patients 1994-2007
1. Anus
2. Hodgkin
3. Lung
4. Liver
5. Breast

EuroSIDA 353 NADM among 14,453 patients (25% women)
Reekie. Cancer 2009

HIV-positive women 2006
1. Breast
2. Lung
3. Hodgkin
4. Cervical
5. Anus
6. Liver

OncoVIH ANRS

Figure 5 The ten most frequently occurring tumours by sex, Belgium 2008
1. Poumon
2. Foie = rein
3. Anus

Achenbach. AIDS 2011
Is the epidemiology of cancer different in HIV-positive women?

- Compared to HIV-negative women
- Compared to HIV-positive men
Meta-analysis of incidence of non-AIDS cancers in HIV+ patients by gender

- Anus
- Skin
- Hodgkin lymphoma
- Stomach
- Lung
- Kidney
- Leukemia
- Larynx
- Melanoma
- Brain
- Multiple myeloma
- Thyroid
- Colon

All non-AIDS cancers

SIR, 95% confidence interval

18 studies
- 9 Europe
- 7 USA
- 1 Australia
- 1 Uganda

From 1981 to 2007

Shiels MS, et al. JAIDS 2009;52:611–22
Focus on

- Breast cancer
- HPV-induced cancers
  - Cervical cancer
  - Anal cancer
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- Breast cancer
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## Saint-Pierre Cohort: NADM SIR

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</tr>
</tbody>
</table>

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
Goedert Br J Cancer 2006
85268 HIV-positive women in USA; 665.987 person-years
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
Why breast cancer could be less frequent in HIV women?

• Hormone production is reduced in HIV: oestradiol or testosterone

• Body composition change with HAART (waist gain)...and the USA obesity epidemics
Why breast cancer could be less frequent in HIV women?

• CXCR4-tropic HIV is protective against breast cancer because
  – In vitro: this receptor is highly expressed by tumor cells and CXCR4 HIV induces tumor cells apoptosis
    Endo M. *Curr HIV Res* 2008
  – In vivo: decreased incidence of breast cancer when compared to CCR5 HIV-infected patients

• Ritonavir has been studied in preclinical trials for its activity against breast cancer growth
Breast cancer

- Survival outcome is comparable to HIV-negative patients secondary to
  - improved immune function
  - early access to cancer screening

  Soji J Surg Oncol 2005

- Myelosuppression secondary to chemotherapy might be enhanced in HIV-patients:
  - Bone marrow deficiency in HIV
  - Drug-drug interaction between cART and chemotherapy
## Rapport Yeni 2010

### Tableau 1. Effet des antirétroviraux sur le métabolisme des médicaments antinéoplasiques

(d'après Antoniou T, Tseng AL [67] et Mounier, Katlama et al. [68] mis à jour)

<table>
<thead>
<tr>
<th>Médicaments antinéoplasiques</th>
<th>Voie métabolique et d'élimination principale</th>
<th>Effet des antirétroviraux sur les concentrations des chimiothérapies associées</th>
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</thead>
<tbody>
<tr>
<td><strong>Antinéoplasiques cytotoxiques</strong></td>
<td><strong>CYP3A majoritaire</strong></td>
<td><strong>Ritonavir</strong> : inhibition importante du métabolisme et augmentation des concentrations des cytotoxiques. Surveiller la tolérance, voire diminuer la posologie</td>
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<tr>
<td><strong>Taxanes</strong> :</td>
<td></td>
<td><strong>IP sans ritonavir</strong> : augmentation modérée des concentrations des cytotoxiques. Surveillance de la tolérance</td>
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<tr>
<td>Docetaxel (Taxotère*)</td>
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<td><strong>INNTI</strong> : diminution modérée des concentrations des cytotoxiques. Conséquences cliniques non évaluées</td>
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<td>Paclitaxel (Taxol*)</td>
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<td><strong>Alcaloïdes de la pervenche</strong> :</td>
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<tr>
<td>Vincristine (Oncovin*)</td>
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<td>Vinblastine (Velbé*)</td>
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<td>Vindesine (Eldésine*)</td>
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<tr>
<td>Vinorelbine (Navelbine*)</td>
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<tr>
<td>Étoposide, VP16 (Vépésiste*)</td>
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<td>Irinotécan (Campto*)</td>
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<td>Ifosfamide (Holoxan*)</td>
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<td>CYP3A4, CYP2B6</td>
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<td><strong>Inhibiteurs de la tyrosine kinase</strong></td>
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<td>Imatinib (Glivec*)</td>
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<td>Sunitinib (Sutent*)</td>
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<td>Sorafenib (Nexavar*)</td>
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<td>Thiotepa</td>
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<td>Tamoxifène (Novaldex*)</td>
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<td>Exemestane (Aromasin*)</td>
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<td>Bortezomib (Velcade*)</td>
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<tr>
<td>CYP3A4 et 2C19</td>
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<td><strong>Corticostéroïdes</strong> :</td>
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<tr>
<td>Prednisone (Solupred*)</td>
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1 Interaction sévère
2 Interaction modérée ainsi ketoconazole :
   + imatinib augmentation des concentrations de + 30 à 40 %;
   + bortezomib + 35 %.
3 Contre-indication avec l’atazanavir qui inhibe l’UGT1A1 qui élimine le métabolite actif SN-38
4 L’importance de l’inhibition peut être diminuée lors de l’association à un PIs induent CYP3A4
# 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>
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<tr>
<td>Breast cancer</td>
<td>Women 50–70 yrs</td>
<td>Mammography</td>
<td>↓breast cancer mortality</td>
<td>1–3 years</td>
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<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>
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<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>
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</table>
Focus on

- Breast cancer
- HPV-induced cancers
  - Cervical cancer
  - Anal Cancer
HPV-induced cancer

- Cervix
- Vulva
- Vagina
- Anal
- Oro-pharyngal
- Penis

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82
THREE-DIMENSIONAL MODEL OF HUMAN PAPILLOMAVIRUS

Major Capsid Protein (L1)

Viral Nucleic Acid (DNA)

© Physicians' Research Network, Inc. All rights reserved.
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
EFFECT OF HIGH-RISK HPV E6 ON THE CELL CYCLE

Normal cells

Cells expressing high-risk HPV E6

DNA damage

G1 arrest

No G1 arrest

G1 arrest

DNA repair

No mutations

No G1 arrest

Genetic instability

Accumulation of mutations

E6-mediated degradation of p53

No p53 accumulation

HIV?

In vitro

Tat protein favors HPV E6+7 expression

Vernon. Virus Res 1993
Human Papillomavirus

- No cell death
- No inflammation
- No antigen presenting cell
- Weak antibody response in 50-90% of persons
- Regression of dysplastic lesions due to cellular immunity against HPV specific antigen (E6 and E7)

Transmission by
- genital contact
- skin contact
- Self inoculation

Reduced by
- Condom
- Circumcision
- Vaccination
The Natural History of HPV Infection and Cervical Cancer

Persistent HPV
- HIV-: 5-10%
- HIV+: 20-40%

Cervical cancer
- HIV-: x 3-11
- HIV+: x 4-10

Vulva & vagina cancer

Infection with oncogenic HPV in HIV women

- Prevalence is higher: 20-40% (vs. 5-10%)

- Multiple genotypes: 40% (vs. 12%)

- New infection? Reactivation of latent infection

- Linked with younger age, lower CD4 and higher HIV VL

Strickler. Journal of the National Cancer 2005
Saint-Pierre Cohort
N=592

Prevalence of HR-HPV infection according to both age and CD4 cell strata (count/µL). ($p=0.03$, logistic regression)
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 (low grade)- SIL

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

¹ Massad. J Acquir Immune Defic Syndr 1999
### Epidemiology of invasive cervical cancer per /100,000 women year

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>2% women</td>
</tr>
<tr>
<td>EU</td>
<td>33,000 new cases/year</td>
</tr>
<tr>
<td></td>
<td>15,000 deaths/year</td>
</tr>
<tr>
<td>Belgium</td>
<td>9.1 /100,000 women/year</td>
</tr>
<tr>
<td></td>
<td>300 deaths/year</td>
</tr>
<tr>
<td></td>
<td>8,300 conisations/year</td>
</tr>
</tbody>
</table>

- HIV patients: SIR invasive cancer x 4-10
Regression of dysplasia

12.5% per year

45% back to normal cytology (vs. 59%)

Recurrence after conisation
Case control study: 68 HIV-positive matched with HIV-negative women

- Normal cytology after conisation ($p<.01$)
  - 33% HIV+
  - 66% HIV-

- % of viral suppression ($p<.01$):
  - Recurrence 20%
  - No recurrence 58%

# 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>

Screening cervical cancer

In Belgium

- Pap-smear reimbursed every 2 years

- HPV screening reimbursed if
  - Previous cancer or dysplasia
  - Current ASCUS
  - Current dysplasia
Longitudinal FU of 855 HIV+ and 343 HIV- women (WHIS)

Table 2. Cumulative Incidence of Any SIL and HSIL+ Among Women With Normal Cytology Results and HPV-Negative at Baseline

<table>
<thead>
<tr>
<th>Baseline HIV and CD4 Count Status</th>
<th>Interval, y</th>
<th>No. at Start of Interval</th>
<th>No. of New SILs</th>
<th>Cumulative Incidence (95% CI)</th>
<th>No. of New HSILs+</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV seropositive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 &lt;200/µL</td>
<td>0-1</td>
<td>61</td>
<td>1</td>
<td>2 (1-9)†</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>42</td>
<td>3</td>
<td>9 (1-18)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>35</td>
<td>7</td>
<td>29 (15-44)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>21</td>
<td>2</td>
<td>37 (20-53)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>16</td>
<td>4</td>
<td>53 (35-71)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 200-500/µL</td>
<td>0-1</td>
<td>180</td>
<td>5</td>
<td>3 (1-6)†</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>155</td>
<td>9</td>
<td>9 (4-13)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>137</td>
<td>7</td>
<td>14 (8-20)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>102</td>
<td>5</td>
<td>18 (12-25)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>92</td>
<td>9</td>
<td>26 (19-34)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 &gt;500/µL</td>
<td>0-1</td>
<td>171</td>
<td>2</td>
<td>1 (1-4)†</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>147</td>
<td>4</td>
<td>4 (1-7)</td>
<td>0</td>
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<tr>
<td></td>
<td>2-3</td>
<td>133</td>
<td>3</td>
<td>6 (2-10)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>111</td>
<td>6</td>
<td>12 (6-17)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>98</td>
<td>1</td>
<td>13 (7-18)</td>
<td>0</td>
</tr>
<tr>
<td>HIV seronegative</td>
<td>0-1</td>
<td>251</td>
<td>4</td>
<td>2 (1-4)†</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>214</td>
<td>3</td>
<td>3 (1-5)</td>
<td>0</td>
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<tr>
<td></td>
<td>2-3</td>
<td>187</td>
<td>4</td>
<td>5 (2-9)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>153</td>
<td>2</td>
<td>7 (3-10)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>135</td>
<td>0</td>
<td>7 (3-10)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HSIL, high-grade squamous intraepithelial lesion; SIL, squamous intraepithelial lesion.
<table>
<thead>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 &lt;200/μL</td>
<td>0-1</td>
<td>48</td>
<td>8</td>
<td>18 (7-29)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>34</td>
<td>11</td>
<td>45 (30-60)</td>
<td>0</td>
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<tr>
<td></td>
<td>2-3</td>
<td>21</td>
<td>4</td>
<td>56 (41-72)</td>
<td>0</td>
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<tr>
<td></td>
<td>3-4</td>
<td>14</td>
<td>4</td>
<td>69 (54-85)</td>
<td>0</td>
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<tr>
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<td>4-5</td>
<td>9</td>
<td>1</td>
<td>73 (58-88)</td>
<td>0</td>
</tr>
<tr>
<td>CD4 200-500/μL</td>
<td>0-1</td>
<td>76</td>
<td>13</td>
<td>18 (9-27)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>57</td>
<td>7</td>
<td>28 (18-39)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>45</td>
<td>8</td>
<td>42 (30-54)</td>
<td>2†</td>
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<tr>
<td></td>
<td>3-4</td>
<td>31</td>
<td>3</td>
<td>48 (35-60)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>26</td>
<td>3</td>
<td>54 (41-67)</td>
<td>0</td>
</tr>
<tr>
<td>CD4 &gt;500/μL</td>
<td>0-1</td>
<td>39</td>
<td>5</td>
<td>13 (2-24)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>32</td>
<td>5</td>
<td>27 (13-42)</td>
<td>0</td>
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<tr>
<td></td>
<td>2-3</td>
<td>24</td>
<td>1</td>
<td>31 (15-46)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>21</td>
<td>2</td>
<td>37 (21-53)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>19</td>
<td>1</td>
<td>41 (24-58)</td>
<td>0</td>
</tr>
<tr>
<td>HIV seronegative</td>
<td>0-1</td>
<td>17</td>
<td>0</td>
<td>0 (0-20)†</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>13</td>
<td>0</td>
<td>0 (0-22)†</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>11</td>
<td>1</td>
<td>11 (1-34)</td>
<td>0</td>
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<tr>
<td></td>
<td>3-4</td>
<td>6</td>
<td>0</td>
<td>11 (1-38)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>5</td>
<td>0</td>
<td>11 (1-41)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSIL+, high-grade squamous intraepithelial lesion or cancer; SIL, squamous intraepithelial lesion.

*Seven of 13 women with CD4 <200/μL, 10 of 20 women with CD4 200-500/μL-500/μL, 3 of 10 women with CD4 >500/μL, and 3 of 5 HIV-seronegative women who were censored for a self-report of having gynecologic treatment had abnormal cervical histology results during the period of observation shown in the table.

†Includes 1 cervical squamous carcinoma.

‡Exact Clopper-Pearson confidence interval.
Cervical screening in USA

- Pap smear and HPV-DNA
- Twice the first year of FU

- If negative: every 1-2/years depending on CD4 level
- If positive: colposcopy and biopsy and frequent FU
Cervical screening in France

- **Pap-smear**
  - Normal
  - Ascus
  - LSIL
  - HSIL
    - HPV neg
      - Check after 1 year
      - Normal
    - HPV pos
      - Check after 6 months
      - Pap-smear after 6 months
        - Colposcopy + biopsy after 1 year
        - Conisation
      - LSIL
        - Colposcopy + biopsy
      - HSIL
Screening in developing countries

• Screen-and-treat approach
• Randomised, n=6555 with 956 HIV-positive women in South Africa, 35-65 years first screen. Excluded macroscopic lesions (6%)
• 3 arm
  – HPV test and cryotherapy
  – Visual inspection+ acetowhite detection and cryotherapy
  – Control: delayed at 6 months
• Women had colposcopy and biopsy at Month 6 (all), 12, 24 and 36 (subset)

<table>
<thead>
<tr>
<th></th>
<th>HIV pos</th>
<th>HIV neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥CIN2 at M36</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Screen HPV RR M36</td>
<td>0.2 (0.06-0.07)</td>
<td>0.3 (0.02-.005)</td>
</tr>
<tr>
<td>Screen VIA</td>
<td>0.51 (0.29-0.89)</td>
<td>p=ns</td>
</tr>
</tbody>
</table>

Kuhn and al. AIDS 2010
Vaccine against HPV

• Gardasil® HPV 6, 11, 16 and 18
• Cervarix ® HPV 16 and 18 (ASO4)

• FDA approval 2006/2009

• In Belgium, reimbursed since end 2007
  - Young girls 12-18 years
  - 3 doses at 0,1-2 et 6 months
  - 420 euros

• Tolerance is excellent

• Protection: 5...10 years?
Vaccine efficiency

- Highly efficient against lesions ≥ CIN2

- \( >90-100\% \ldots \)
  - if no contacts with vaccine HPV genotypes (ie, before first sexual contacts)
  - And if induced by these serotypes...

- 30-45% if previous contacts (after sexual contacts)

- against lesions induced by non vaccinal but related type to HPV 16 (ie, HPV 31/33/45/52/58) or to HPV 18 (ie, HPV 45) (=20 percent of cervical cancers)
  - 20% Gardasil
  - 50% Cervarix
HPV vaccination

**Recommendation**

- **WHO**
  - Vaccination girls 9-13

- **USA**
  - Vaccination girls 11 to 12-18
  - Catch up vaccination 13 to 26 (but cost-effectiveness...)
  - Males 9-26
  - MSM
What about HIV-patients?


Meta-analysis in HIV-women with HSIL: 18, 33, 51, 52, 58

11, 52, 61

Vaccine against HPV in HIV patients

Gardasil®

Immunogenicity

Safety

No effect on CD4 nor VL

- in HIV-seropositive boys and girls aged 7 to 12.

Antibodies titers against HPV 6 and 18 was 30-50% decreased compared to HIV-negative patients

Levin. J Acquir Immune Defic Syndr. 2010

- in HIV-seropositive men, without previous or present anal infection with vaccinal types

Wilkin. J Infect Dis. 2010

- Studies on efficacy are ongoing in USA in MSM
Vaccine against HPV in HIV women?

- Vaccinate girls? yes
- Vaccinate boys: yes but in Belgium...cost?

- Young women:
  - No efficacy data in HIV-positive for Gardasil
  - No safety data nor efficacy for Cervarix
  - Cost
Focus on

- Breast cancer
- HPV-induced cancers
  - Cervical cancer
  - Anal Cancer
Age-adjusted incidence rates (per 1,000,000 persons) of in situ and invasive anal cancer among women, 1973–2005.


© 2009 by the Infectious Diseases Society of America
Invasive cancer
SIR 6-8 (in USA, St-Pierre Cohort)

Piketty
AIDS 2008
132 cases of invasive anal cancer among 86322 HIV-patients
Median survival 5 years
Anal Cancer in HIV women

- All HPV 75% (46% if no anal receptive intercourse)
- HR-HPV 44% (vs. 17%)
- Abnormal anal cytology: 26% (vs. 8%) 35%
  HG-AIN: 6% (vs. 2%) 5%
  Holly. Conley
  *J Natl Cancer Inst. JID*
  2001 2010

- Frequently associated with cervical dysplasia, low CD4 count (and high viral load) and receptive anal intercourse and Nb HR-HPV
- Effect of HAART? Conflicting results
• Anal screening should be implemented
  – High-resolution anoscopy
Anal cancer

- Treatment: role of imiquimod
  - 3 times per weeks/4 months
  - Favorable outcome (clearance or regression to AIN1) compared to placebo (p=.003)

Fox. AIDS 2010

- Vaccination: Preventive and Therapeutic vaccines
Anal cancer: Vaccination

- Immuno-therapeutic Vaccination: Induce Ab response and Cytotoxic T cell response
- HPV-16 E6E7
- Randomised, double-blind, placebo-controlled
- 3 doses 0.5 ml at Day 1, 14/30, 70/90
- Safety: moderate to severe short term reaction 5/35 had transient VL
- Strong and durable Ab response
- Moderate IFN G response that lasted 6 months
- Not powered to detect clinical efficacy

Anderson. J Acquir Immune Def Syndr 2009
In summary

- NADM have become a major problem for HIV-women because of aging
- Breast cancer is not increased by HIV-infection but incidence could increase after restored immunity
- HPV-induced cancers are not reduced after cART introduction
- Screening should be improved for cervical cancer and implemented for anal cancer
- Preventive vaccination against HPV should be more extensively studied and applied in HIV women