MALIGNANCIES IN HIV

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Disclosure

I have no conflict of interest to declare in relation with this presentation
Outline

• General consideration on HIV & cancer
• Hepatocellular carcinoma
• Lung cancer
• Breast cancer
• Colorectal cancer
• Chemotherapy and HAART
• HPV and cancer
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 viruses: HPV (Anal), HBV and HCV (Liver), EBV (HL)
  ➢ Not linked with (identified) viruses
All cancer crude and standardized incidence rates by HIV status and calendar period and P values for incidence rate period trend.

HIV+, HIV-infected; IR, incidence rate

AIDS, July 2016, Vol 30 No 11
Most important risk factors for NADC

- Increasing age
- Smoking
- Co-infection with oncogenic viruses:
  - Epstein Barr
  - HPV
  - HHV8
  - HBC
  - HCV
Others risk factors for NADC

• Length of time since HIV diagnosis / lower nadir CD4

• Irreversible and persistent disruption and damage in lymphoïd tissues, despite effective viral suppression and improved levels of circulating CD4

• Role of ART remains controversial (anal cancer, Hodgkin’s lymphoma?)
Role of Natural Killer Cells in HIV-Associated Malignancies
Non AIDS malignancies

- 34% of causes of death in France in the cART era
- Relative risk highly variable:
  - Anal cancer: RR: 47
  - Hodgkin lymphoma: RR: 19
  - Lung cancer: RR: 3.5
  - Liver cancer: RR: highly dependent of the frequency of HCV co-infection

Impact of age is minimal except for liver cancer (11 y younger)

Early HIV treatment and CD$_4$ >500 seem to reduce RR for lung cancer but not for the 3 others
Hepatocellular carcinoma

- Incidence rate 3-6 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
Hepatocellular carcinoma

- Screening recommended for co-infected patients
- HCV clearance does not abrogate the risk but attenuates it by 50-75%

**GUIDELINES**

**Screening for hepatocellular carcinoma**
- Ultrasound (US) every 6 months
  - Alpha-fetoprotein is a suboptimal surveillance tool because of low sensitivity and specificity
- In case of suspicious lesions on US, perform CT scan (+arterial phase) or dynamic contrast-enhanced MRI
- Confirm diagnosis by fine needle aspiration or biopsy should CT scan or MRI be inconclusive

**Treatment:**
- Liver transplantation
- Resection
- Radiofrequency ablation
Lung Cancer

- Diagnosed at younger age with advanced disease and primarily in smokers
- Adenocarcinoma is the most frequent sub-type
- No argument to treat differently than non-HIV infected patients
- No clear screening strategy

Should general population recommendations be extended to HIV patients? (i.e. LDCT between 55-80 y, with >30 pack year history, active smokers or stopped in the past 15 years)
Lung Cancer :
The Kaiser Permanente study

- Crude lung cancer rate / 100,000 p-y (HIV pos vs neg): 66 vs 33
  - Unadjusted: RR 2.0 (1.7 - 2.2)
  - After adjustment for demographic characteristics: RR 1.9 (1.5 - 2.4)
  - After additional adjustment for smoking/drug/alcohol/overweight: RR 1.4 (1.1 - 1.7)
  - After full adjustment including prior pneumonia: RR 1.1 (0.9 - 1.5)

- HIV pos patients with recent CD4 (cells/µl)
  - > 500 ➔ no excess risk in unadjusted and adjusted models
  - < 500 ➔ excess risk if not adjusted for pneumonia

(Marcus et al, AIDS, 2017)
Lung Cancer:
The Kaiser Permanente study

- Increased risk of lung cancer among HIV-infected individuals is attributable to differences in demographic characteristics, cancer risk factors such as smoking and pneumonia.

- Immunodeficiency does not have an independent effect on lung cancer risk in this population.

- HIV patients with pneumonia may be good candidates for lung cancer screening.

- Smoking cessation efforts, early antiretroviral therapy initiation, and pneumococcal vaccination and Pneumocystis jiroveci chemoprophylaxis may reduce the burden of lung cancer in this population.

(Marcus et al, AIDS, 2017)
Smoking cessation in HIV patients

- Cancers are a major source of morbidity and mortality in HIV+ persons in the context of available treatment, due to longer life expectancy, reduced immune function and behavioural factors.
- The prevalence of smoking in HIV+ persons is 40–70%.
- Excess mortality due to smoking in HIV+ persons is ~ 3-fold higher than in the general population, driven by cardiovascular and malignancy related deaths.
- The incidence of most cancers, including lung, increase with older age. As the HIV+ population ages, smoking cessation is one of the few proven modifiable risk factors.
- The clinical benefits of smoking cessation on cancer risk have not been reported for HIV+ persons.

Smoking cessation in the general population

- The decline in cancer incidence with longer time since cessation is well established in the general population
- Reduction in incidence varies by cancer type
- Lung cancer risk is halved after 10 years of cessation

Smoking cessation in the HIV + population
Adjusted Rate Ratios for specific cancers (D:A:D)

Models were adjusted for age, gender, transmission group, race, BMI, calendar year, treatment, CD4, HIV viral-load, hepatitis B and C status, AIDS defining events (excluding cancers), anaemia, hypertension, and duration of smoking.
Smoking cessation in HIV patients

• Lung cancer remains elevated in HIV+ persons many years after cessation, indicating that the health impacts of smoking remain long after cessation

• This trend is specific to lung cancer and indicates an ongoing oncogenic process that are not seen for other smoking related cancers and smoking unrelated cancers

• Smoking cessation efforts should be a priority to reduce the risk of cancer, however, surveillance and screening of lung cancer should not be stopped in those who stop smoking
Breast Cancer

- Frequency approaching that of the general female population
- Greater likelihood of multifocal breast involvement
- More advanced stage at diagnosis
- Possibly lesser response to systemic chemotherapy
- No specific recommendations for screening
Colorectal cancer

- Third most common cancer and leading cause of death from cancer in PLWHA

- Conflicting data on relation risk and on severity of disease

- Application of guidelines of the general population to PLWHA seems reasonable
HAART and chemotherapy

• Many patients will receive HAART and chemotherapy concurrently with high likelihood of drug interactions and overlapping toxicities.

• Many antiretroviral agents are substrates and/or 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.
DD interactions: other mechanisms

- **UDP Glucuronosyltransferase 1** metabolizes several ARV’s such as PI’s and maraviroc and antineoplastic drugs such as irinotecan and etoposide

- **P-glycoprotein efflux pump (or MDR1 or ABCB1)** plays a vital role in absorption and cellular transfert of PI’s and cytotoxics such as vinca alkaloids, taxanes, doxorubicin and etoposide

- Expression of CYP 450, UDP-G1 and Pgp is determined by numerous genetic polymorphisms
HPV and cancer in HIV patients
HPV: Human Papilloma Virus

Small DNA virus that induces the development of tumor

- benign or condyloma or genital warts (Low risk genotypes HPV 6/11)

- Cancer (High risk or oncogenic HPV):
  - Anal cancer
  - Cervical cancer

16, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

70%

90%

HIV Summer School
Aug 30 - Sept 3, 2018
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
The burden of HPV infections and induced lesions in HIV + 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 is 3 (cervix and OPC) to 40 (anal) times higher than in the general population
    - Robbins H. 2015
  - Among all cancers diagnosed in HIV patients, 15% are HPV-related (vs 4,5%)
Why is HPV an issue in HIV + patients?

1. The burden of HPV-related disease is tremendously increased in HIV-positive patients

2. Mortality is high
   - D:A:D (Europe, Australia, USA): 42,000 persons from 2004 to 2010: 3 years mortality of anal cancer 31% (85% died of their cancer)
   - Worm S. BMC infect Dis 2013

3. Screening for HPV-induced cancers may be difficult
   - Cervix: technique well described but not always implemented
   - Anus: technique is more a matter of debate and high resolution anoscopy is difficult to implement
   - Oral cancer: no screening available

4. High rates of recurrence after treatment
How to prevent HPV-infection and induced lesions?

• Condom/circumcision: partial protection

• **Screening for cancer**
  – Cervix
  – Anus

• cART

• **HPV vaccination**
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
Does cART prevent HPV infection and HPV-induced lesions in HIV + women?

<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Year</th>
<th>n</th>
<th>Follow-up</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minkoff . JID 2010</td>
<td>n= 286</td>
<td>30 months</td>
<td>Decrease HPV prevalence from 22 to 14%, Decrease SIL incidence and prevalence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Konopnicki D. JID 2013</td>
<td>n= 652</td>
<td>61 months</td>
<td>Undetectable HIV RNA for &gt; 40 months or CD4 &gt; 350-500 &gt; 18 months Decreases the risk of persistent HR HPV</td>
<td></td>
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<tr>
<td>Adler D. AIDS 2012</td>
<td>n= 1123</td>
<td>66 months</td>
<td>Decreases SIL incidence Increases SIL regression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blitz S. JID 2013</td>
<td>n=750</td>
<td>24 months</td>
<td>Decreases HR HPV prevalence Increases SIL regression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeier M. AIDS 2015</td>
<td>n=300</td>
<td>22 months</td>
<td>Each month on cART decreases the risk of: any HPV 9% (0.89-0.94) HPV16 50% (0.37-0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen Y. AIDS 2014</td>
<td>n= 1360</td>
<td>2000-2008</td>
<td>cART associated decreases risk of cervical cancer 0.20 (0.05-0.77) &amp; 0.01 (0.00-0.47) if 85% adherence and &gt;3 years of cART</td>
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<tr>
<td>Konopnicki D.</td>
<td>n= 766</td>
<td>41 months</td>
<td>Undetectable HIV RNA for &gt; 37 months or CD4 &gt; 350-500 &gt; 17 months decreases risk of SIL</td>
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Large longitudinal cohorts With several years of follow up different clinical endpoints
Does cART prevent HPV infection and HPV-induced lesions in HIV + men?

**Longitudinal study n=247 MSM on cART since 22 months, FU 61 months**
de Pokomandy. *CID* 2011.

**Cross-sectional study n=250 MSM, CD4 490, nadir 229, 80% cART since 7 years**
Van der Snoeck E. *Sex transm Dis* 2012.

**Cohort, n= 311, 89% under cART (median =9 years)**
Richel O. *PLoSOne* 2013

**American veterans cohort: retrospective analysis, n= 45,000, 377 with anal cancer, 1985-2009**

**Retrospective study n=1654**
Duncan K. *AIDS* 2015

**Cross-sectional study**
n=320 MSM, cART since 5 years
Libois A. *Sex Transm Infect* 2016

**Patients with cART >4 years have decreased risk of HGAIN (OR=0.28; 95%CI:0.07-1.06)**

**Decreased HPV and AIN if cART**

**Inverse correlation between duration of cART and AIN (-8%/year)**

**Anal cancer decreases if HIVRNA is undetectable >60% of time vs <20% (odds ratio, 0.56; P = 0.040)**

**Time to anal cancer shorter if treated before HAART-era (AHR=3.04 (1.48-6.24), p=.002) suggesting that HAART slows down progression from AINHG to cancer**

**Patients with cART≥ 2 years had decreased risk of HSIL (OR=0.32; 95%CI:0.16-10.63)**

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Does cART prevent HPV infection and HPV-induced lesions in HIV + men?
## Prophylactic Vaccine

<table>
<thead>
<tr>
<th></th>
<th>Bivalent (2vHPV)</th>
<th>Quadrivalent (4vHPV)</th>
<th>Ninevalent (9vHPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV Genotypes</strong></td>
<td>16/18</td>
<td>16/18 + 6/11</td>
<td>16/18/31/33/45/52/58 + 6/11</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td>ASO4 monophosphoryl lipid A = detoxified derivative of LPS of Salmonella adsorbed on aluminium</td>
<td>Aluminium</td>
<td>Aluminium</td>
</tr>
<tr>
<td><strong>FDA/EMA approval</strong></td>
<td>2007</td>
<td>2006</td>
<td>2014/15</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Precancerous lesions and cancer in the cervix, vulva or vagina and anus</td>
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</tr>
<tr>
<td><strong>Vaccination dosing</strong></td>
<td>0 and 6 months &lt; 15 years 0, 1 and 6 months if ≥15 years</td>
<td>0 and 6 months &lt; 15 years 0, 2 and 6 months if ≥15 years</td>
<td>0 and 6 months &lt; 15 years 0, 2 and 6 months if ≥15 years</td>
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HPV preventive vaccines in HIV+ patients

9 studies (7 4vHPV/1 2vHPV/ 1 comparing 4vHPV and 2vHPV)

- 1500 subjects
- Children
- Young women and women (up to 60 years)
- MSM
- Good CD4 levels or under cART

- **Good immunogenicity and anamnestic response**
- **Good safety: less local reaction**
- **No deleterious effects on CD4 levels nor on viral load control**
- **Induction of cellular immune response**

against HPV16 in 60% (3 doses), 72% (4 doses) (QHPV)
against HPV16/18 (specific CD4+T cells response) 82% (BHPV)

Wilkin. *JID* 2010
Kahn J. *CID* 2013
Kojic E. *CID* 2014
Giacomet V. *Vaccine* 2014; Rainone V. *AIDS* 2015
Torfs L. *CID* 2014
Denny L. *Vaccine*. 2013
Money D. *Vaccine* 2016
Hidalgo-Tenorio. *AIDS Res Ther* 2017
Which vaccine to use in HIV+ patients?

<table>
<thead>
<tr>
<th></th>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>2vHPV</td>
<td>Higher level of antibody: clinical meaning? Longer protection? Less doses?</td>
<td>No protection against condyloma</td>
</tr>
<tr>
<td></td>
<td>Cross-protection HPV 31/33/45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kavanagh K. Lancet Infect Dis 2017</td>
<td></td>
</tr>
<tr>
<td>4vHPV</td>
<td>Protection against genital warts</td>
<td>• Price</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Availability?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 70% of cancer</td>
</tr>
<tr>
<td>9vHPV</td>
<td>Largest protection against cancer (90%) and condyloma genotypes</td>
<td>Price</td>
</tr>
</tbody>
</table>
How many doses in HIV+ patients? Guidelines / Recommandations

- **EACS:**
  - Vaccinate with 3 doses for all HIV-positive persons up to age 26 / age 40 if MSM (health insurance coverage differs by country according to age, sex, sexual orientation). Use 9-valent vaccine if available.
  - If HPV infection is established, efficacy of vaccine is questionable.

- **BHIVA:** 3 doses
  - in Adults, 9vHPV (or 4vHPV), MSW or women up to 26 y, MSM up to 40 y

- **WHO:** first girls and if achieved then males and females ≥ 15 y any age with HIV infection even if treated: 3 doses
  - Preference of which vaccine according to local price/HPV distribution

- **ACIP:** 3 doses
  - from 9 to 26 y to all persons with HIV
  - MSM and transgender: up to 26