Malignancies in HIV

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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
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
Incidence of first NADM (with 95% CI) stratified by different indicators of immunosuppression

- **Latest CD4 (cells/mm\(^3\))**
  - <100 - 200 - 300 - 400 - 500 - 500

- **Lagged CD4 (cells/mm\(^3\)), 6 months**
  - <100 - 200 - 300 - 400 - 500 - 500

- **Nadir CD4 (cells/mm\(^3\))**
  - <100 - 200 - 300 - 400 - 500 - 500

- **Time-averaged CD4 (cells/mm\(^3\))**
  - <100 - 200 - 300 - 400 - 500 - 500
Incidence of first NADM (with 95% CI) stratified by duration of immunosuppression (years)

Rate /100 PYRS

0,4

0,8

1,2

1,6

2

2,4

<200 cells/mm³

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

<100 cells/mm³

RR /year: 1.05 (1.03, 1.07), p=0.0001

Years, duration of immunosuppression
Incidence of first NADM (with 95% CI) stratified by indicators of viraemia

**Latest HIV RNA**

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

**AUC for HIV RNA**

- RR /unit: 1.04 (1.00, 1.09), p=0.07
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
Cancer group standardized incidence rates (per 100,000 person-years) by HIV status and calendar period, standardized incidence rate ratios with 95% confidence intervals by period, and P values for standardized incidence rate ratio period trend.

ADC, AIDS-defining cancer; HIV+, HIV-infected; IR, standardized incidence rate; IRR, standardized incidence rate ratio; NADC, nonAIDS-defining cancer; Nonvirus-NADC, nonvirus-related nonAIDS-defining cancer; Virus-NADC, virus-related nonAIDS-defining cancer. Note that Y-axis scale varies by cancer group.
Non AIDS malignancies

- Disparities in access to care and to treatment in the US (not in France)
- Cancer specific mortality higher in HIV patients in the US (HR ranging from 1.28 (lung) to 2.64 (breast) for different cancer, after adjustment for cancer treatment)

- But: Is it linked to HIV status or to demographic and social issues?
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
  - Breast cancer: RR: <1
  - Prostate cancer: RR: <1

- 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
Hodgkin disease

• 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

- 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 similar as in HIV negative patients, including transplantation.
Hepatocellular carcinoma

- Screening recommended for co-infected patients

- HCV clearance does not abrogate the risk but attenuates it by 50-75%

Treatment:
- Liver transplantation
- Resection
- Radiofrequency ablation

GUIDELINES

Screening for hepatocellular carcinoma
- Ultrasound (US) every 6 months
  Alpha-foetoprotein 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
Lung cancer
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 is possible, 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
Summary of the Proposed Mechanisms Linking HIV With Lung Cancer

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<th>Theory</th>
<th>Mechanisms</th>
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<td>Direct oncogenic effect of HIV</td>
<td>Virus-inducing microsatellite alterations and widespread genomic instability.</td>
<td>Wistuba et al&lt;sup&gt;43&lt;/sup&gt;</td>
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<td><em>Tat</em>, an essential gene for HIV-1 replication, increases expression of</td>
<td>el-Solh et al&lt;sup&gt;44&lt;/sup&gt;</td>
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<td>protooncogenes and proliferation of the human adenocarcinoma cell line</td>
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<td>by downregulating tumor suppressor gene p53.</td>
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<td>Downregulation of HIV <em>Tat</em>-interacting protein (TIP30) has been found</td>
<td>Baker et al&lt;sup&gt;46&lt;/sup&gt;</td>
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<td>to promote metastasis of lung cancer.</td>
<td>Tong et al&lt;sup&gt;46&lt;/sup&gt;</td>
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<td>HIV-induced immunosuppression</td>
<td>Conflicting evidence, wherein immunosuppression may lead to a reduction in</td>
<td>Bower et al&lt;sup&gt;15&lt;/sup&gt;</td>
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<td>tumor surveillance, thus enabling tumor growth.</td>
<td>Engels et al&lt;sup&gt;47&lt;/sup&gt;</td>
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<td>Chronic inflammation</td>
<td>Chronic inflammation has been recognized as a risk factor for lung cancer.</td>
<td>Engels&lt;sup&gt;48&lt;/sup&gt;</td>
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<td>Individuals with HIV infection and chronic pneumonia and asthma are</td>
<td>Shebl et al&lt;sup&gt;49&lt;/sup&gt;, Kirk et al&lt;sup&gt;50&lt;/sup&gt;</td>
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<td>at higher risk of lung cancer.</td>
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<td>The rate of pneumonia is nearly six times higher in patients with HIV</td>
<td>Sogaard et al&lt;sup&gt;50&lt;/sup&gt;</td>
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<td>infection and CD4 counts &gt; 500 cells/µL than in control subjects without HIV.</td>
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<td>Cigarette smoking</td>
<td>Smoking is an independent risk factor for lung cancer in individuals with</td>
<td>Guiguet et al&lt;sup&gt;58&lt;/sup&gt;</td>
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<td>HIV infection.</td>
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<td>Smoking is two to three times more prevalent among individuals with HIV</td>
<td>Engels et al&lt;sup&gt;58&lt;/sup&gt;, Giordano and Kramer&lt;sup&gt;51&lt;/sup&gt;</td>
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<td>infection than in the general population.</td>
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<td>IV drug use</td>
<td>IV drug users with HIV infection have an increased risk of lung cancer</td>
<td>Serraino et al&lt;sup&gt;52&lt;/sup&gt;</td>
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<td>compared with nonusers with HIV.</td>
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*Tat* = transactivator of transcription.
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
Lung cancer and age

- Incidence higher in men but relative risk compared with the general population is higher in women

- Prospective screening of lung cancer by CT Scan poorly effective in HIV patients below 55 y of age
- Insufficient data to recommend lung cancer screening with low dose CT in asymptomatic persons
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
Use of antineoplastic agents in cancer patients with HIV/AIDS

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Abstract

In the era of highly active antiretroviral therapy (HAART), patients with human immunodeficiency virus (HIV) have reduced morbidity and mortality of AIDS-related complications. However, there is an increase in the prevalence of AIDS-defining and non-AIDS-defining cancers. This article provides an up-to-date review of management of HAART pharmacotherapy in the context of cytotoxic chemotherapy or targeted antineoplastic agents.
HPV and cancer in HIV patients
Persistent Infection

5-10% If HIV negative

20-30% If HIV positive
Cervical Intraepithelial Neoplasia

**HISTOLOGY (BIOPSY)**

- **CIN I**: 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.

**Smear**

- **LG-SIL** Squamous Intraepithelial Lesions
- **HG-SIL**
- **CYTOLOGY (Smear)**
HPV-induced cancers

- Cervix
- Anus
- Vagina
- Vulva
- Penis

- Oro-pharyngal

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

➢ Clinical level

Vernon. Virus Res 1993
Tugizov. Virology 2013
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

**CD4 cell count decreases**
**HIV Viral load increases**
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:

- How? High resolution anoscopy and histology (cytology for triage): Training, material, side effects

- Who? 
  - MSM: Incidence cancer 80/100,000 persons-year
  - Women: Incidence cancer 16/100,000 persons-year
  - Prevalence of ≥AIN2: 9% (2001-06) Hessol. AIDS 2009

- Should Anal screening be implemented for all women?

- Natural history of AIN could differ from CIN

Does cART prevent HPV infections or HPV-induced lesions?

- **NO**
  - **Design**: N
  - **Endpoints**: Duration of cART
  - **Palefsky**: Cross-S before <100 anal HPV prev. 6 months
  - **JAIDS 2001**
  - **Paramsothy**: Longitudinal 537 cervical HPV & SIL 24 months
  - **Obstet & Gyn 2009**: Decreased progression and increased regression of SIL but p=ns
  - **Shrestha**: Longitudinal 100 cervical HPV 14 months
  - **BMC Inf Dis 2010**: Incidence

- **YES**
  - **Design**: N
  - **Endpoints**: Duration of cART
  - **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 and of cytological abnormalities
Konopnicki D. JID 2013

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

- Younger than 30: 3.13 times higher chance
- CD4 count above 500 for more than 18 months: 12% lower chance
- Viral load below 50 copies for more than 40 months: 19% lower chance
What about HPV prevention?
**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
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
Levin. J AIDS. 2010
Wilkin. JID 2010
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
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