EACS HIV Summer School
5-9 September 2016
Aix-en-Provence, France

Malignancies in HIV

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iris

HIV and cancer

- AIDS-defining malignancies:
  - Kaposi's sarcoma
  - Non Hodgkin lymphoma 1985
  - Cervical cancer 1993

HHV8
EBV
HPV

- 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

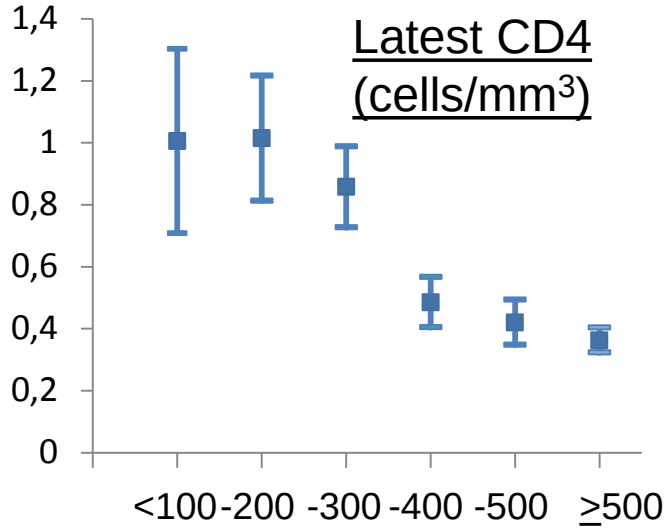
  - MSM have nearly double the rate of tobacco use compared to all U.S. men: 48% vs 29% (Stall 1999)

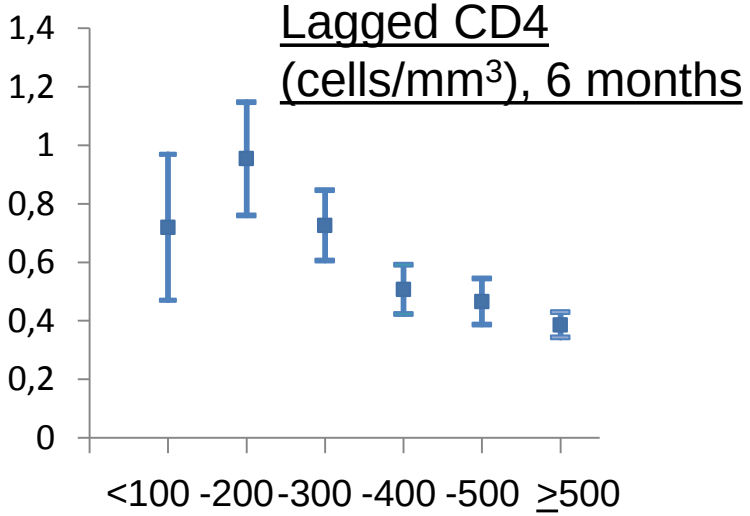
  - A role of HIV through its effect on immune deficiency

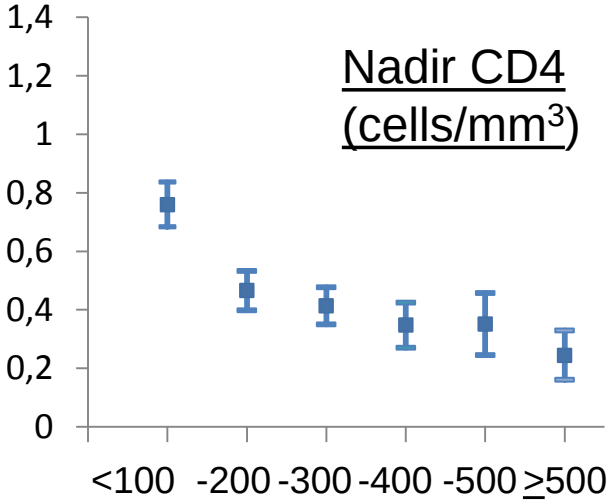
  Importance:

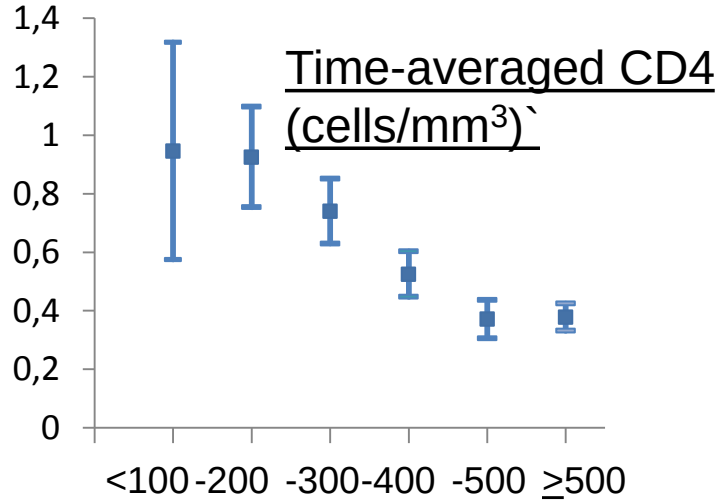
  - If immune deficiency is responsible, then reversing immune deficiency might decrease cancer risk

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

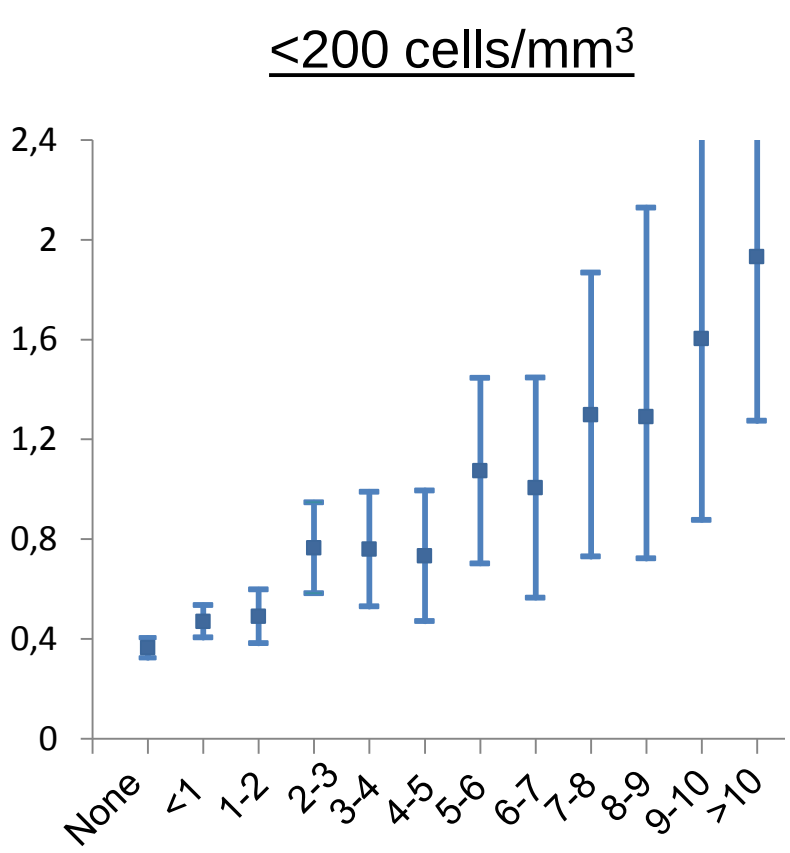




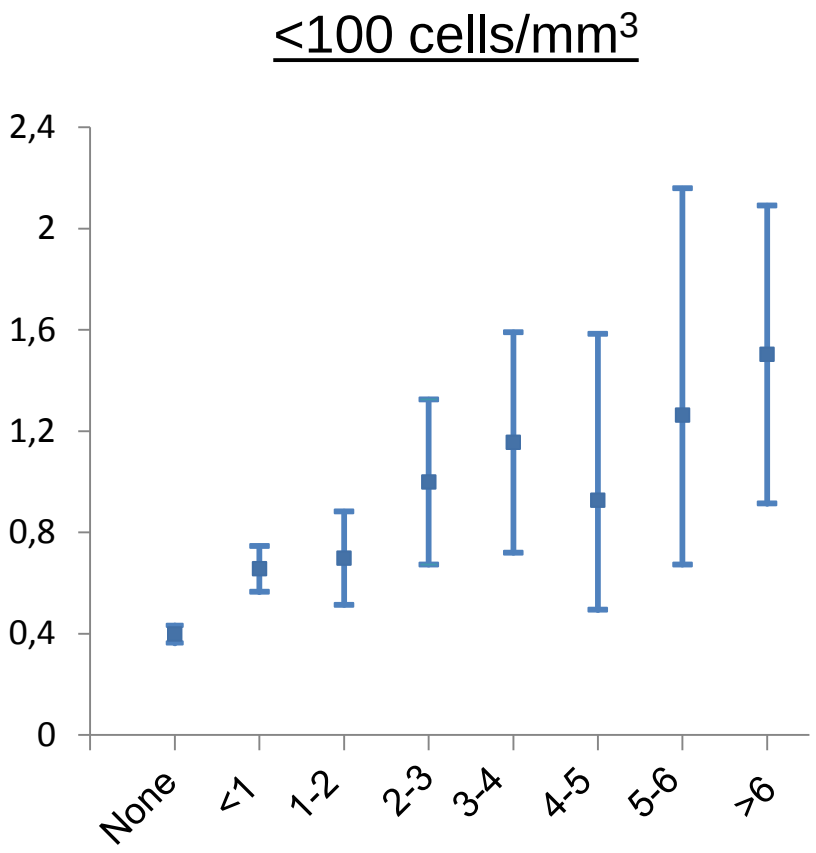




Incidence of first NADM (with 95% CI) stratified by duration of immunosuppression (years)



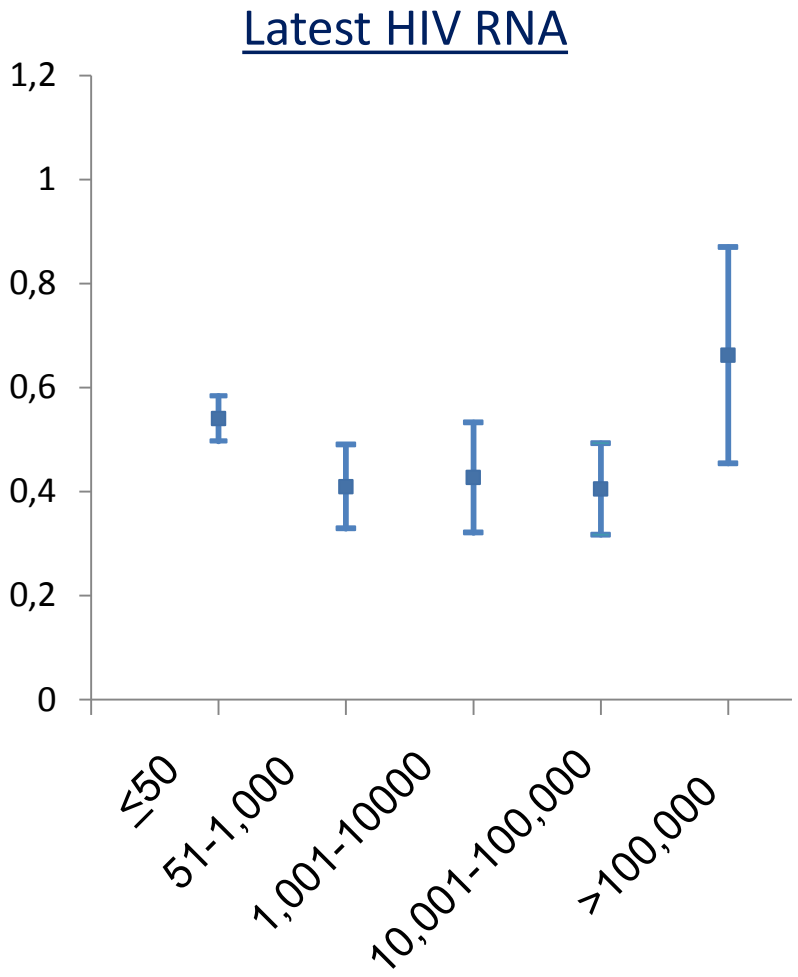
RR /year: 1.05 (1.04, 1.06), p=0.0001



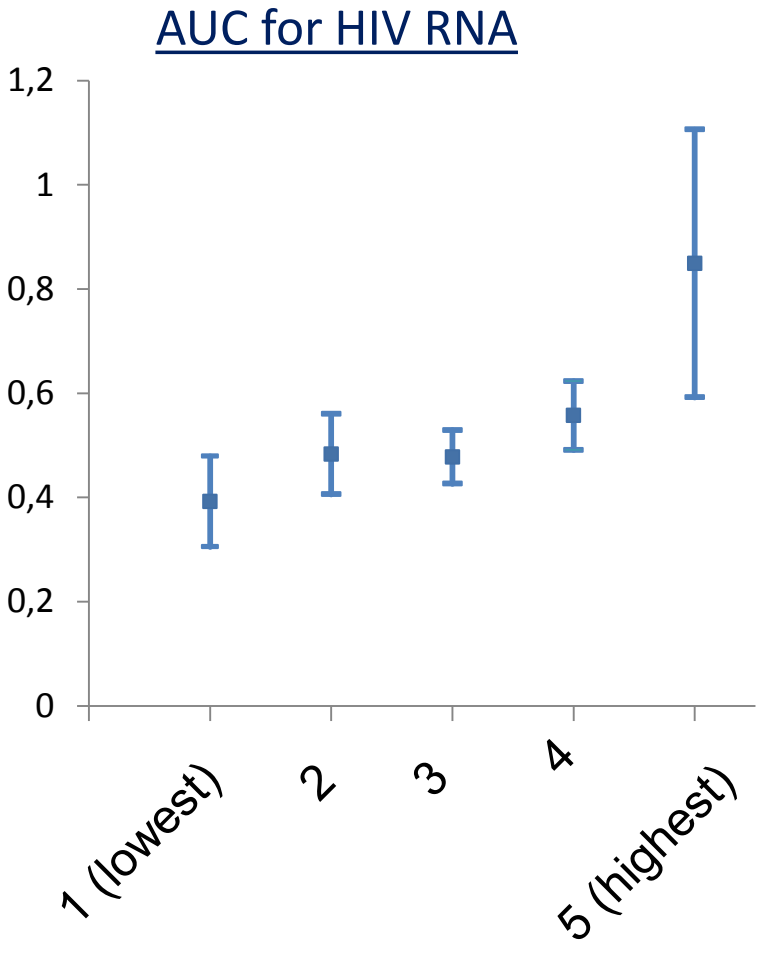
RR /year: 1.05 (1.03, 1.07), p=0.0001

Years, duration of immunosupression

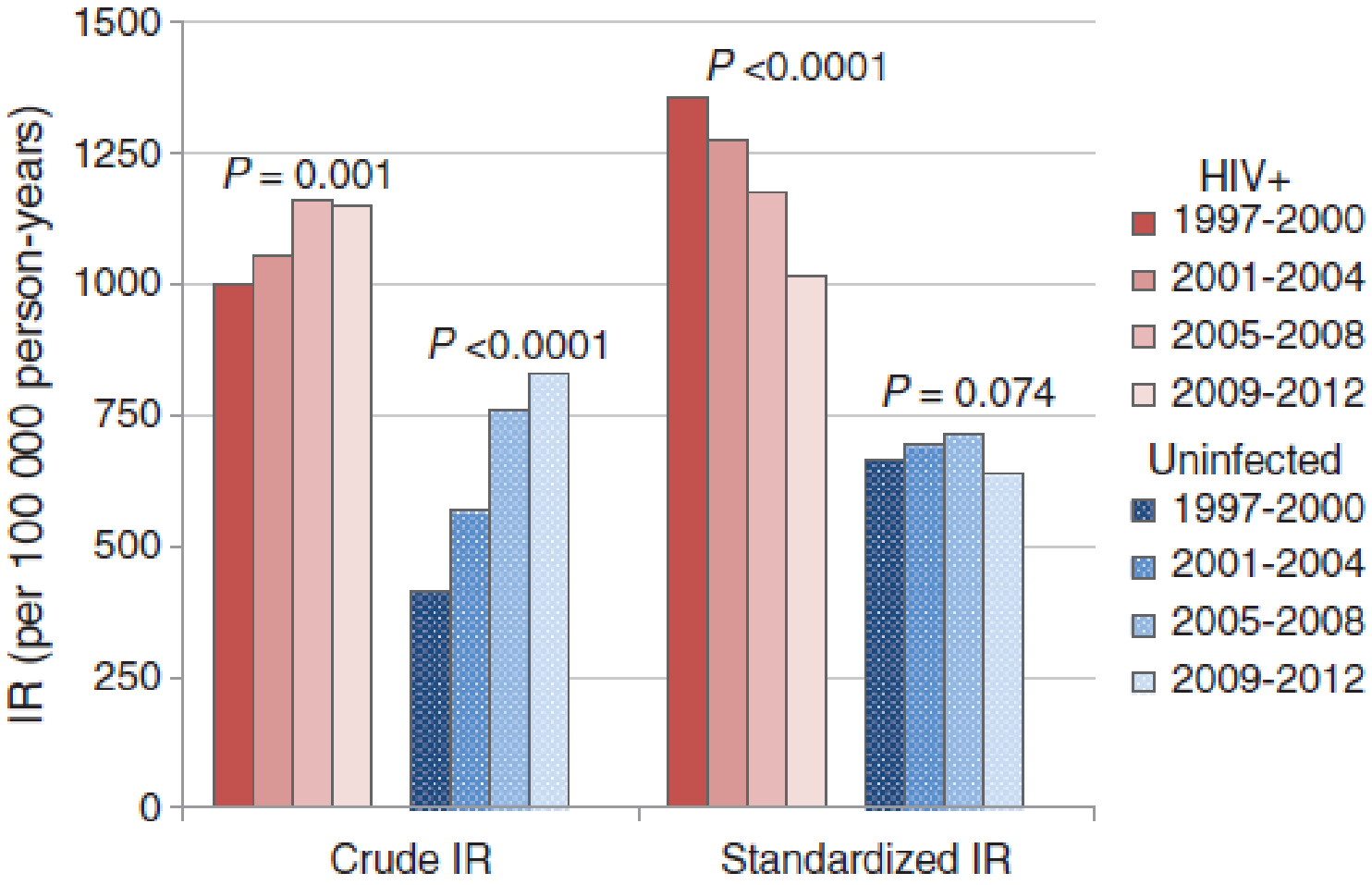
Incidence of first NADM (with 95% CI) stratified by indicators of viraemia



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

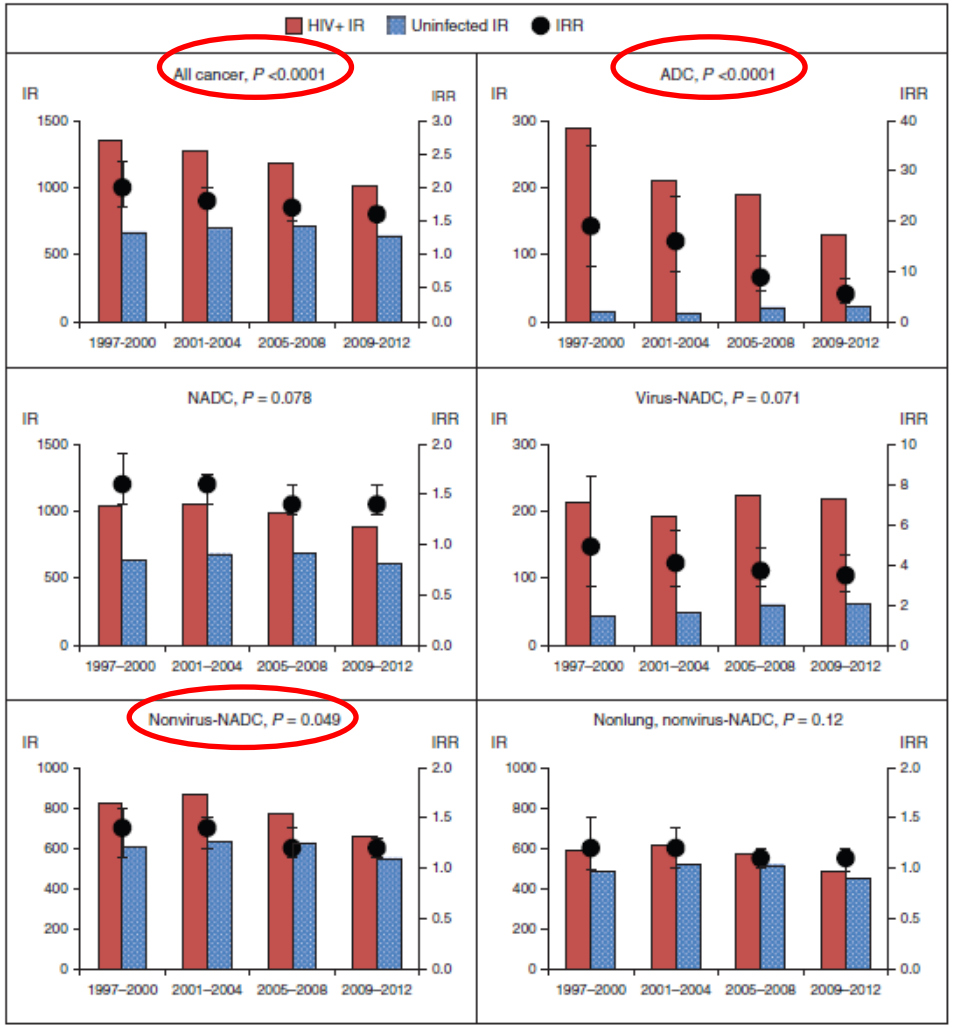


All cancer crude and standardized incidence rates by HIV status and calendar period and P values for incidence rate period trend.

HIV+, HIV-infected; IR, incidence rate

All Cancers

ADC



NADC

Virus NADC

Non-virus NADC

Non-virus NADC, Lung excluded

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; HIVþ, 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 nonAIDSdefining cancer. Note that Y-axis scale varies by cancer group.

Veterans Aging Cohort, Park et al, AIDS, July 2016, Vol 30 No 11

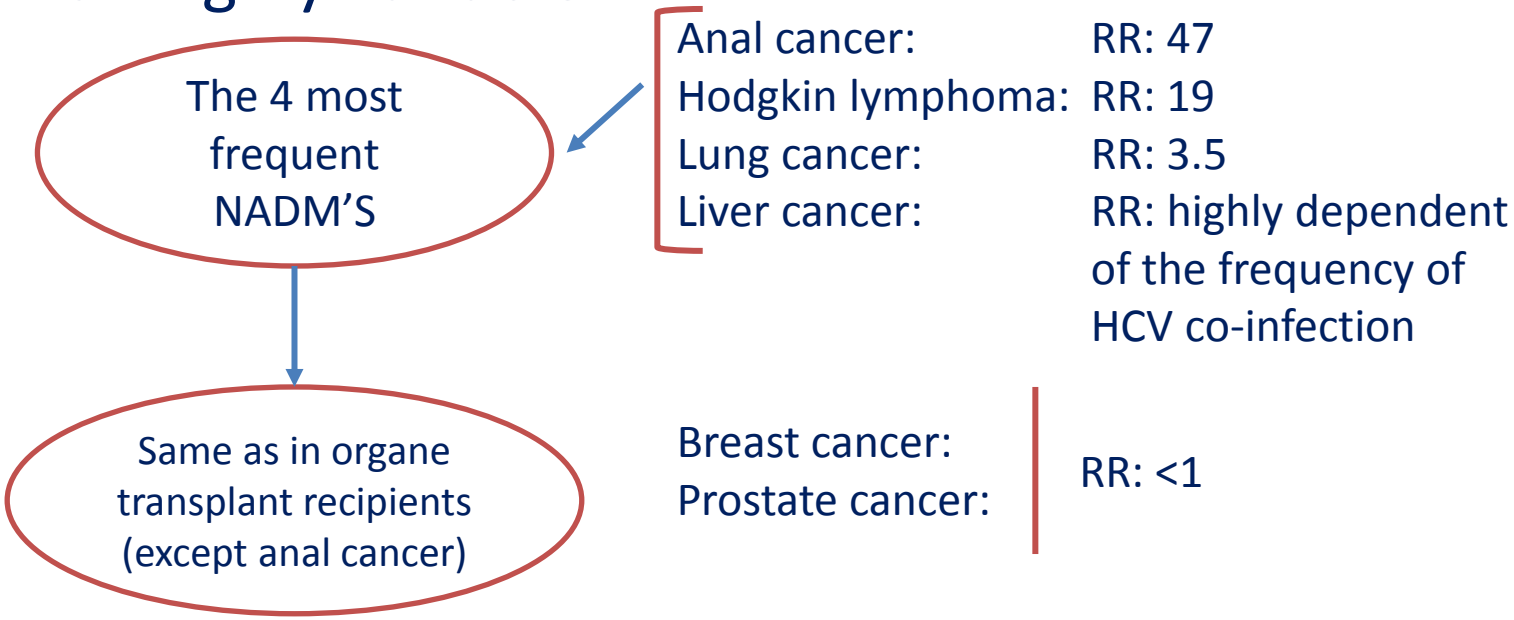
Non AIDS malignancies

- 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?

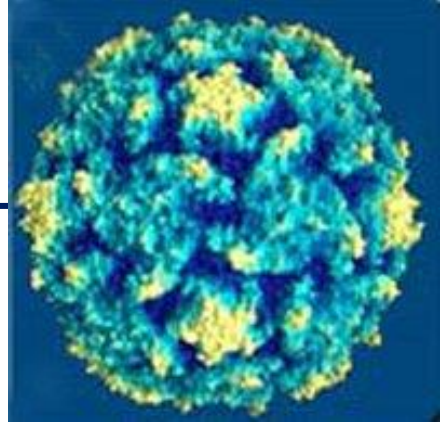
Non AIDS malignancies

- 34 % of causes of death in France in the cART era
- Relative risk highly variable:



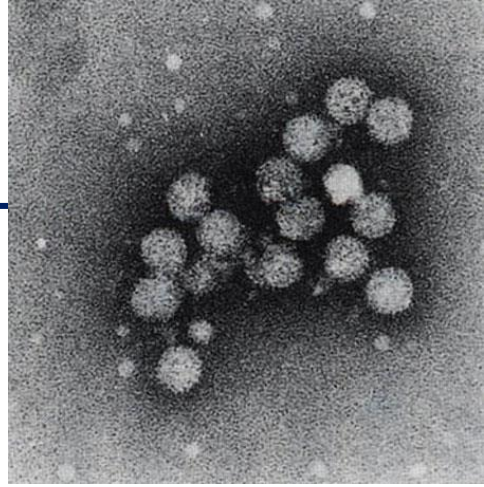
- Impact of age is minimal except for liver cancer (11 y younger)
- Early HIV treatment and CD_4 >500 seem to reduce RR for lung cancer but not for the 3 others

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%

EACS European AIDS Clinical Society

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

- Treatment:
  - ➢ Liver transplantation
  - ➢ Resection
  - ➢ Radiofrequency ablation

Lung cancer

Excess of risk of lung cancer in HIV

- Hypothesies 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

Theory	Mechanisms	Key References
Direct oncogenic effect of HIV	Virus-inducing microsatellite alterations and widespread genomic instability.	Wistuba et al[43]
	Tat, an essential gene for HIV-1 replication, increases expression of protooncogenes and proliferation of the human adenocarcinoma cell line by downregulating tumor suppressor gene p53.	el-Solh et al[44]
	Downregulation of HIV *Tat*-interacting protein (TIP30) has been found to promote metastasis of lung cancer.	Baker et al,[45] Tong et al[46]
HIV-induced immunosuppression	Conflicting evidence, wherein immunosuppression may lead to a reduction in tumor surveillance, thus enabling tumor growth.	Bower et al,[15] Engels[47]
Chronic inflammation	Chronic inflammation has been recognized as a risk factor for lung cancer.	Engels[48]
	Individuals with HIV infection and chronic pneumonia and asthma are at higher risk of lung cancer.	Shebl et al,[49] Kirk et al[41]
	The rate of pneumonia is nearly six times higher in patients with HIV infection and CD4 counts >500 cells/μL than in control subjects without HIV.	Sogaard et al[50]
Cigarette smoking	Smoking is an independent risk factor for lung cancer in individuals with HIV infection.	Guiguet et al[28]
	Smoking is two to three times more prevalent among individuals with HIV infection than in the general population.	Engels et al,[18] Giordano and Kramer[51]
IV drug use	IV drug users with HIV infection have an increased risk of lung cancer compared with nonusers with HIV.	Serraino et al[52]

Tat = transactivator of transcription.

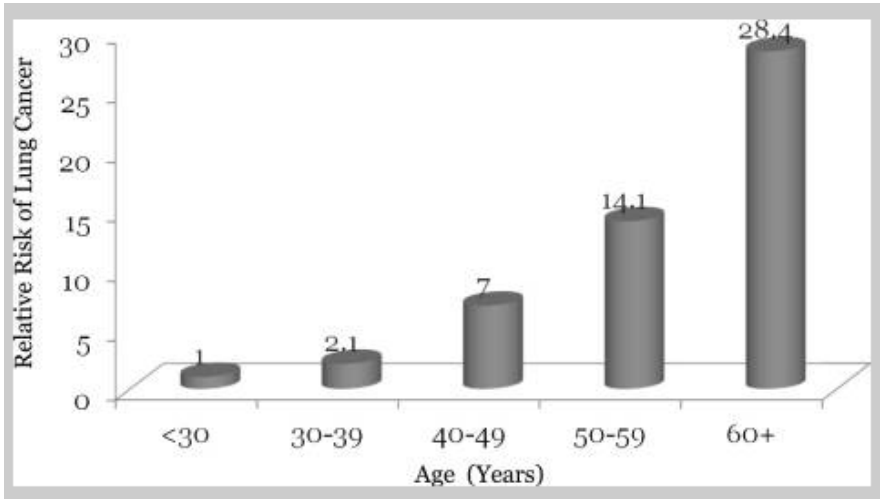
Chest, February 2013, 143/2

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

Lancet Oncol. 2011 September ; 12(9): 905–912. doi:10.1016/S1470-2045(11)70056-0.

Use of antineoplastic agents in cancer patients with HIV/AIDS

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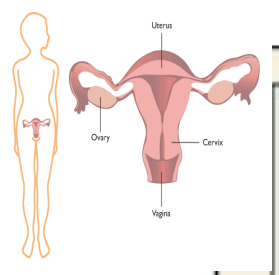
Abstract

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



Viral persistence and progression

Normal cervix

HPV-infected cervix

Precancerous lesion

Cancer

Clearance

Regression

Invasion

HPV

Persistent Infection

5-10% If HIV negative

20-30% If HIV positive

Precancer

Cancer

15 years

30 years

45 years

Pap tests

HPV vaccination

HPV test 1

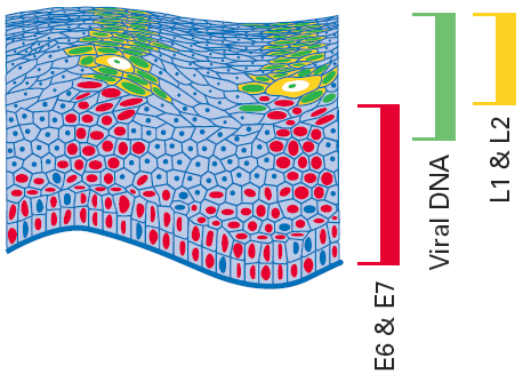
HPV test 2

Schiffman, M. et al. N Engl J Med 2005;353:2101-2104

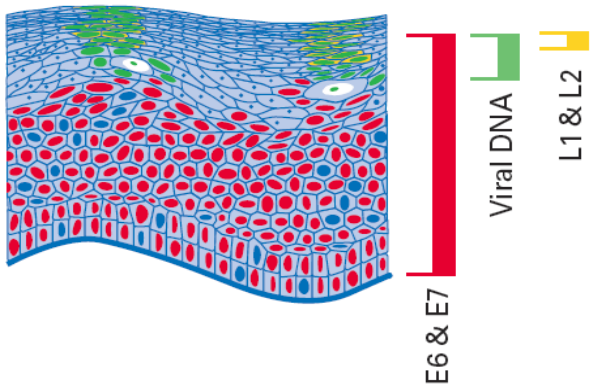
Cervical Intraepithelial Neoplasia

HISTOLOGY (BIOPSY)

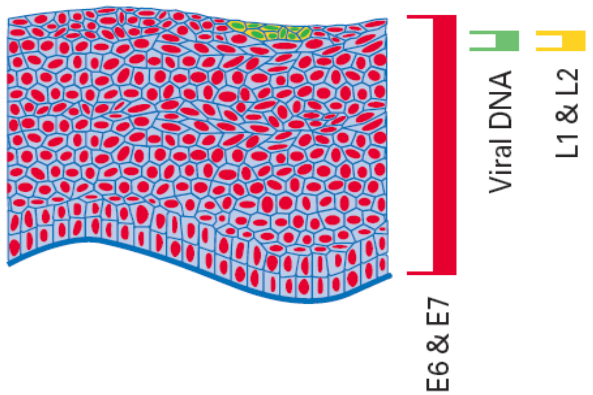
CIN I [and Warts]:
Mild dysplasia, lower one-third of epithelium
The full complement of HPV DNA and proteins (Early and Late) are produced. Infectious virus is produced in the mature squamous cell layer.



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)**

HPV-induced cancers

- Cervix
- Anus
- Vagina
- Vulva
- Penis

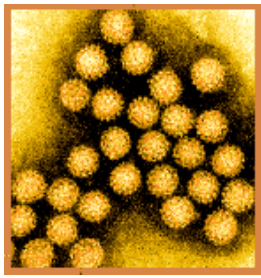
- Oro-pharyngal

70% sk HPV genotypes:

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

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

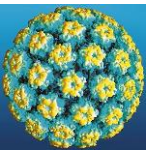
Tugizov. Virology 2013

➢ Clinical level

The burden of HPV infections and induced lesions in HIV-positive patients

CD4 cell count decreases
HIV Viral load increases

- **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 dysplasic 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



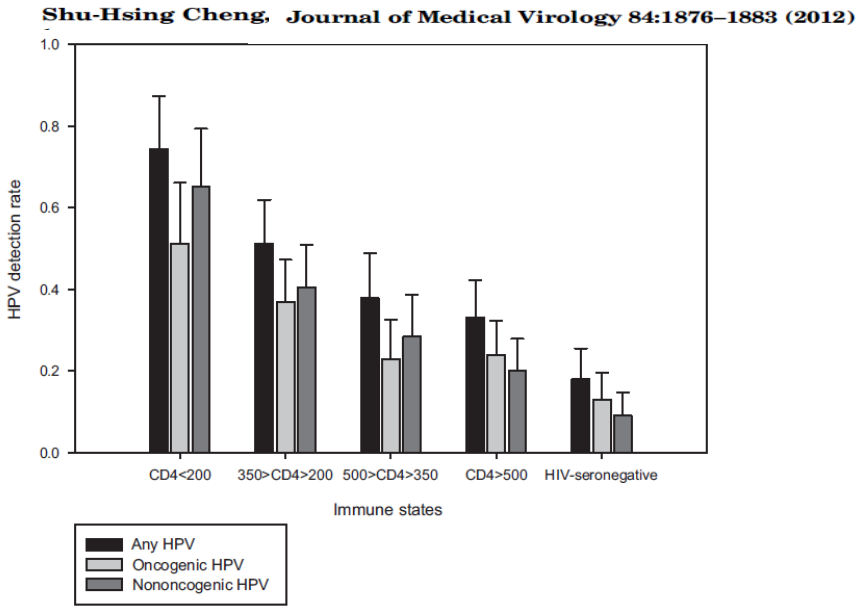
Screen and treat approach in limited resource setting

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:***

Does cART prevent HPV infections or HPV- induced lesions?

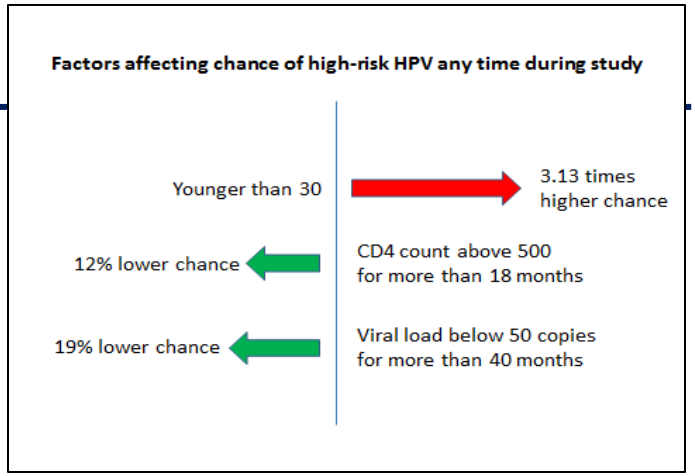
…more recently

FEMALE

Cohort of 652 women, 38 years,
successfully treated for HIV,
FU 61 months

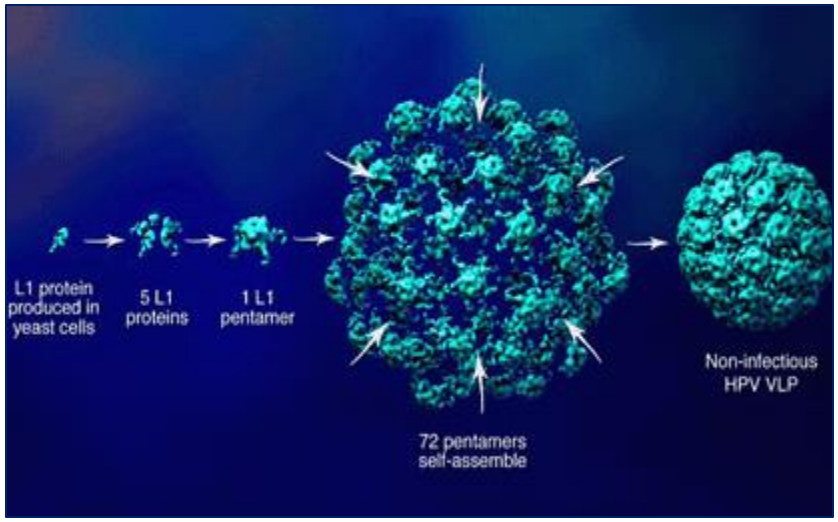
Sustained viral suppression and higher CD4 T cell reduces the risk of persistent HRHPV and of cytological abnormalities

Konopnicki D. *JID 2013*



What about HPV prevention?

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

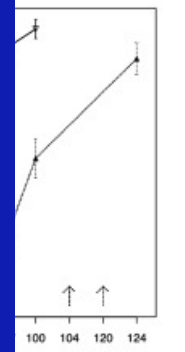
Levin. *J AIDS.* 2010
Wilkin. *JID* 2010
Kahn J. XIX International AIDS Conference. Washington 2012. WEAB0202
Kojic E. XIX International AIDS Conference. Washington 2012. WEAB0203

Studies on clinical efficacy ?

Phase IV 2010-2015:
Thailand, Brazil, USA

Gardasil vs Cervarix
in women 15-25 years

ongoing



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Biv

ne. 2013

- ***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%

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**