HIV Summer School
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MALIGNANCIES IN HIV

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Disclosure

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

Outline

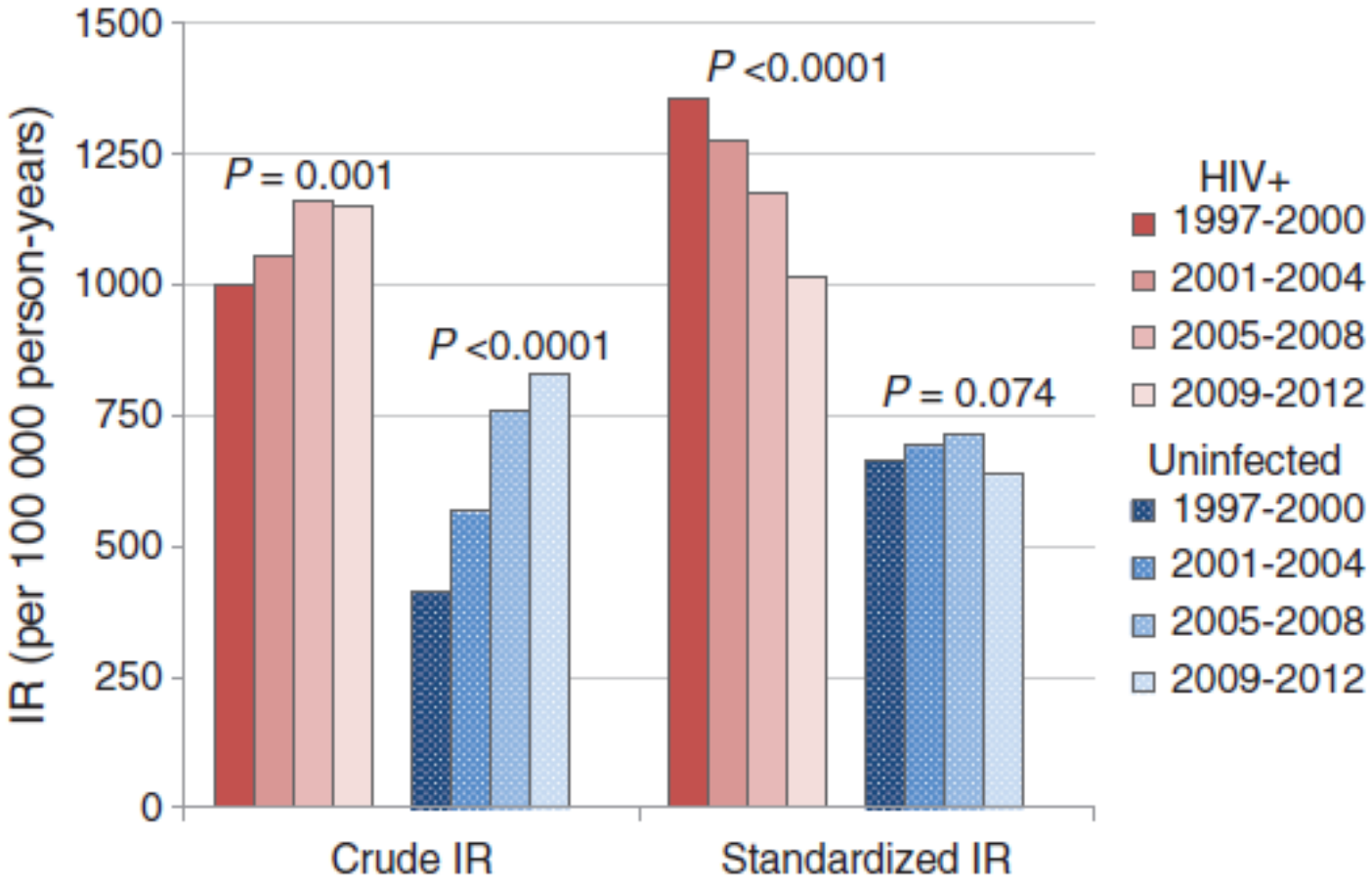
- General consideration on NADM's
- Hepatocellular carcinoma
- Lung cancer
- Breast cancer
- Colorectal cancer
- Chemotherapy and HAART
- HPV and cancer

HIV and cancer

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

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



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

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

Increased rates of nADCs. Why ?

Other possible explanations:

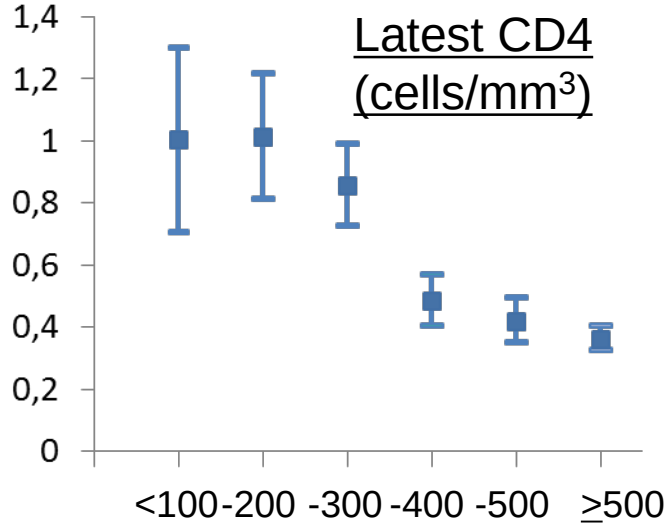
- Confounding by shared lifestyle cancer risk factors

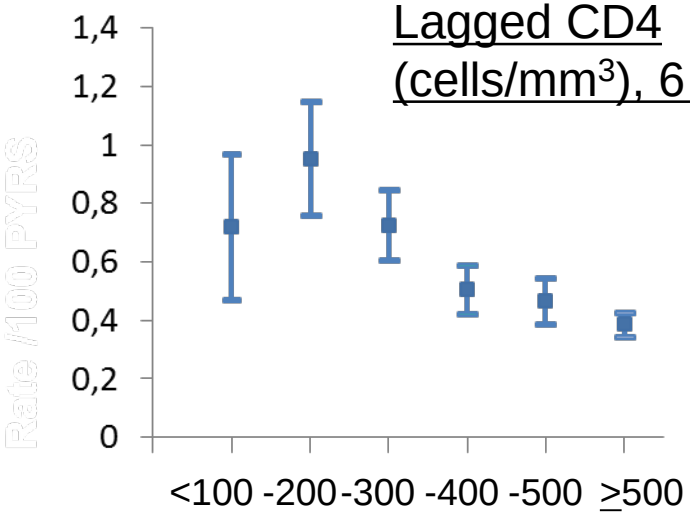
  Tobacco use

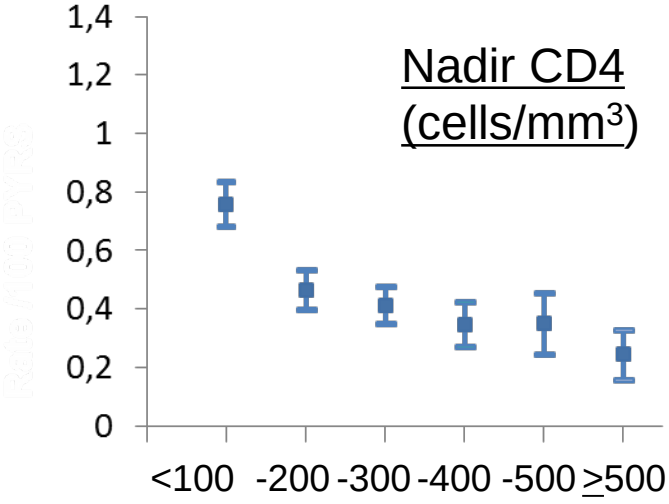
  - HIV US patients (especially MSM have more than double rate of tobacco use compared to U.S. general population: 42,4% vs 20,6% (Mdodo & al 2015)

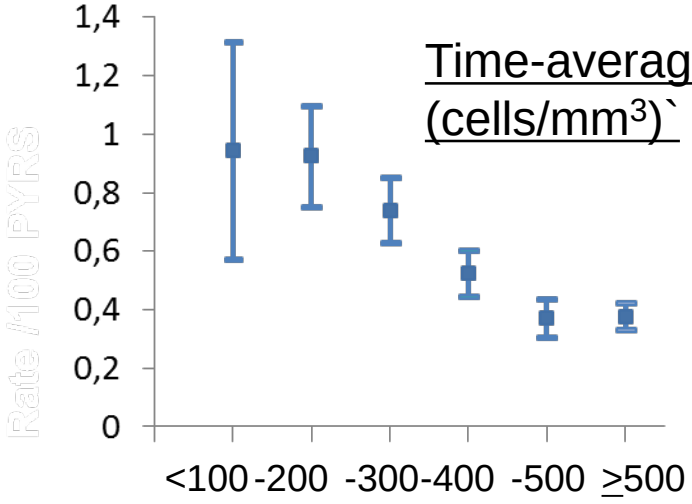
  - A role of HIV through its effect on immune deficiency, directly or indirectly

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



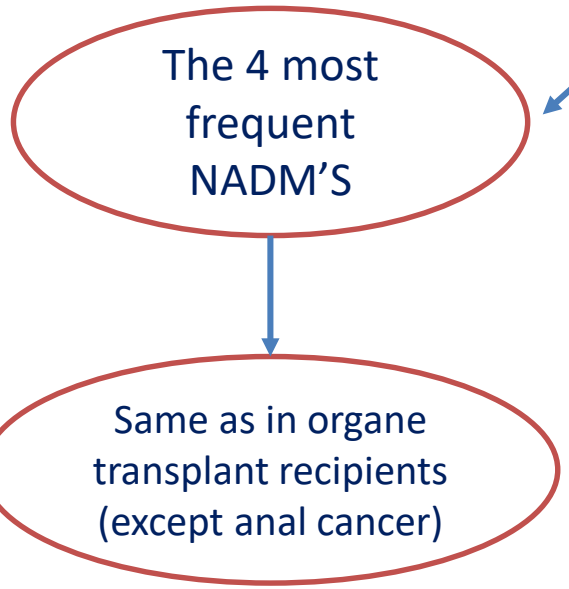






Non AIDS malignancies

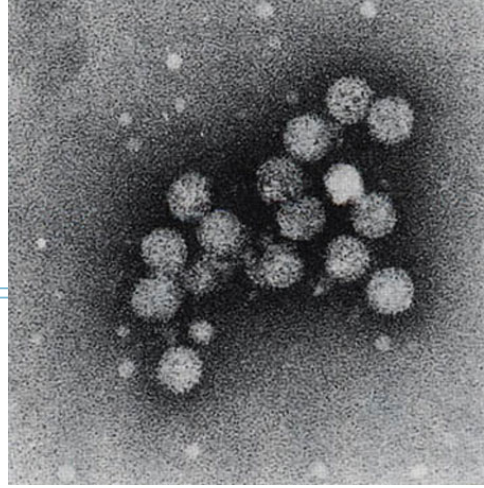
- 34 % of causes of death in France in the cART era
- Relative risk highly variable:



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
- Treatment similar as in HIV negative patients, including transplantation.

Hepatocellular carcinoma

- Screening recommended for co-infected patients
- In HBV co-infection, risk is mainly linked to cirrhosis and TDF free regimens
- 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 (L.C): The Kaiser Permanente study

- Crude L.C 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 CD_4 (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 (L.C): The Kaiser Permanente study

Conclusion:

1. Increased risk of lung cancer among HIV-infected individuals is attributable to differences in demographic characteristics, cancer risk factors such as smoking, and pneumonia, but immunodeficiency does not have an independent effect on lung cancer risk in this population

2. HIV patients with pneumonia may be good candidates for lung cancer screening, and 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)

Lung Cancer

- Diagnosed at younger age with advanced disease and primarily in smokers
- Adenocarcinoma is most frequent sub-type
- No argument to treat differently than non-HIV infected patients
- In a meta analysis of 12 cohort studies, pooled RR of mortality was 1,5 compared to HIV neg population
- 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)

Smoking cessation

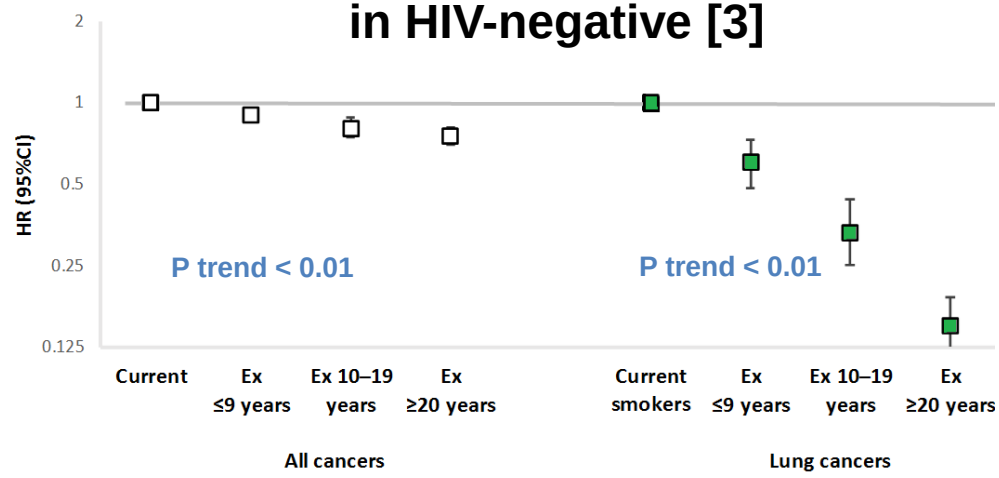
- The prevalence of smoking in HIV+ persons is > 40 % [2]
- Excess mortality due to smoking in HIV+ persons is ~ 3-fold higher than in the general population, driven by cardiovascular and malignancy related deaths [3]
- About 25% of cancers in the HIV + population are related to smoking, i.e. lung, head & neck, esophagus and bladder.
- The incidence of most cancers, including lung, increase with older age. Therefore, as the HIV+ population age, smoking cessation is one of the few proven modifiable risk factors [4]
- The clinical benefits of smoking cessation on cancer risk have not been reported for HIV+ persons

1. Smith *et al* 2014, Lancet;2. Browning *et al* 2013, Clin Chest Med; 3. Helleberg *et al* 2013 CID; 4. Hasse *et al* 2011, CID

Smoking cessation in the HIV-negative population

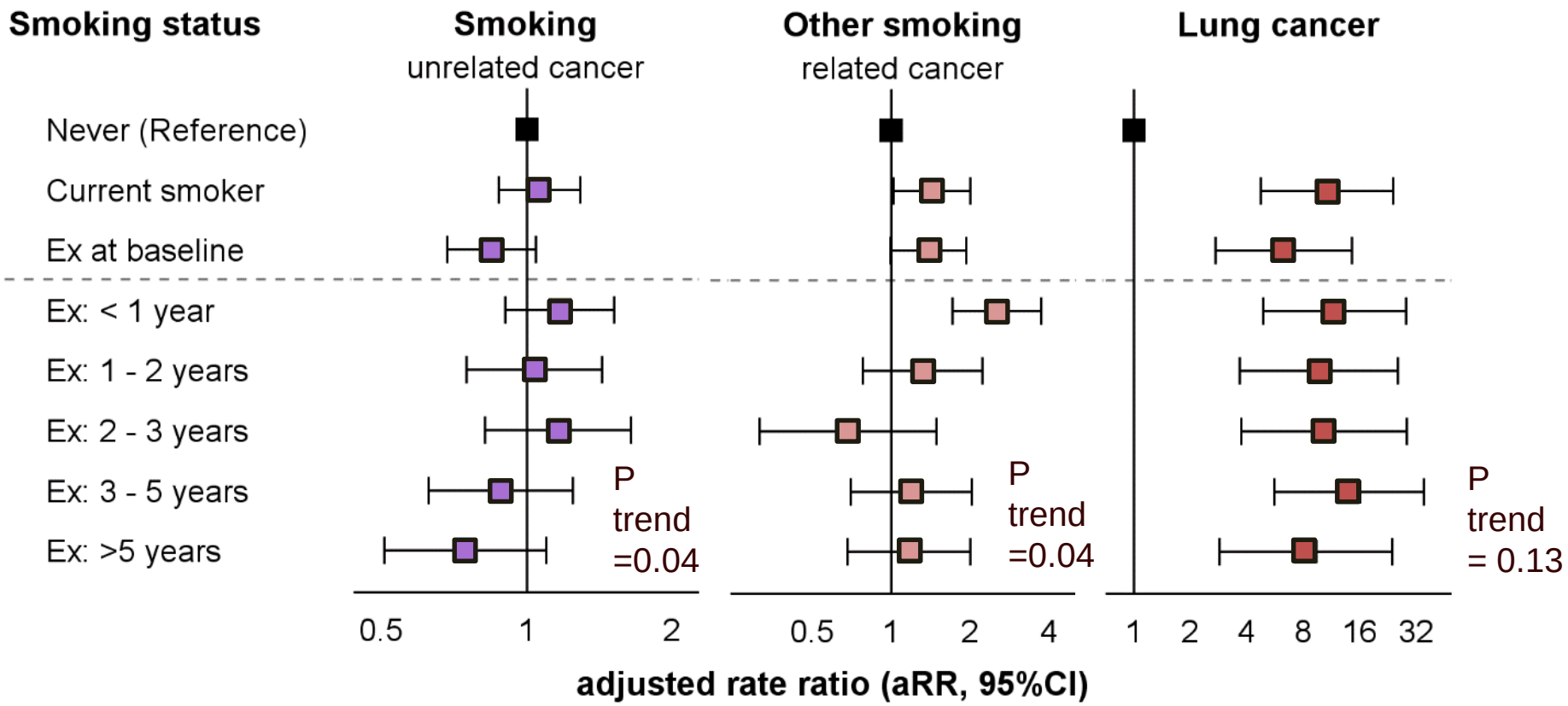
- The decline in cancer incidence with longer time since cessation is well established in the HIV-negative population [1][2]
- Lung cancer risk is halved after 10 years of cessation [1][2]
- Reduction in incidence varies by cancer type [2]

HR for cancer incidence by years since cessation in HIV-negative [3]



1. Fry *et al* 2013, Regulatory Toxicology and Pharmacology,
2. US Surgeon General, 1990 US Surgeon General;
[3] Ordóñez-Mena, 2016, BMC medicine

Adjusted Rate Ratios for specific cancers



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: summary

- 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
- Younger median age (46 vs 61 years)
- 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

Cancer screening in the HIV population

- Systematic review on the topic:
  - 613 papers
  - 9 fulfilled eligibility criteria (all from US)
  - 4 on colorectal, 3 on breast, 2 on prostate
  - 5 papers showed lower acces to screening compared to general population, 3 better access, 1 same rate.
  - Access clearly linked to access to care.

HAART and chemotherapy

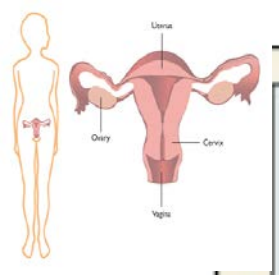
- Many patients will receive HAART and chemotherapy concurrently with high likelihood of drug interactions and overlapping toxicities

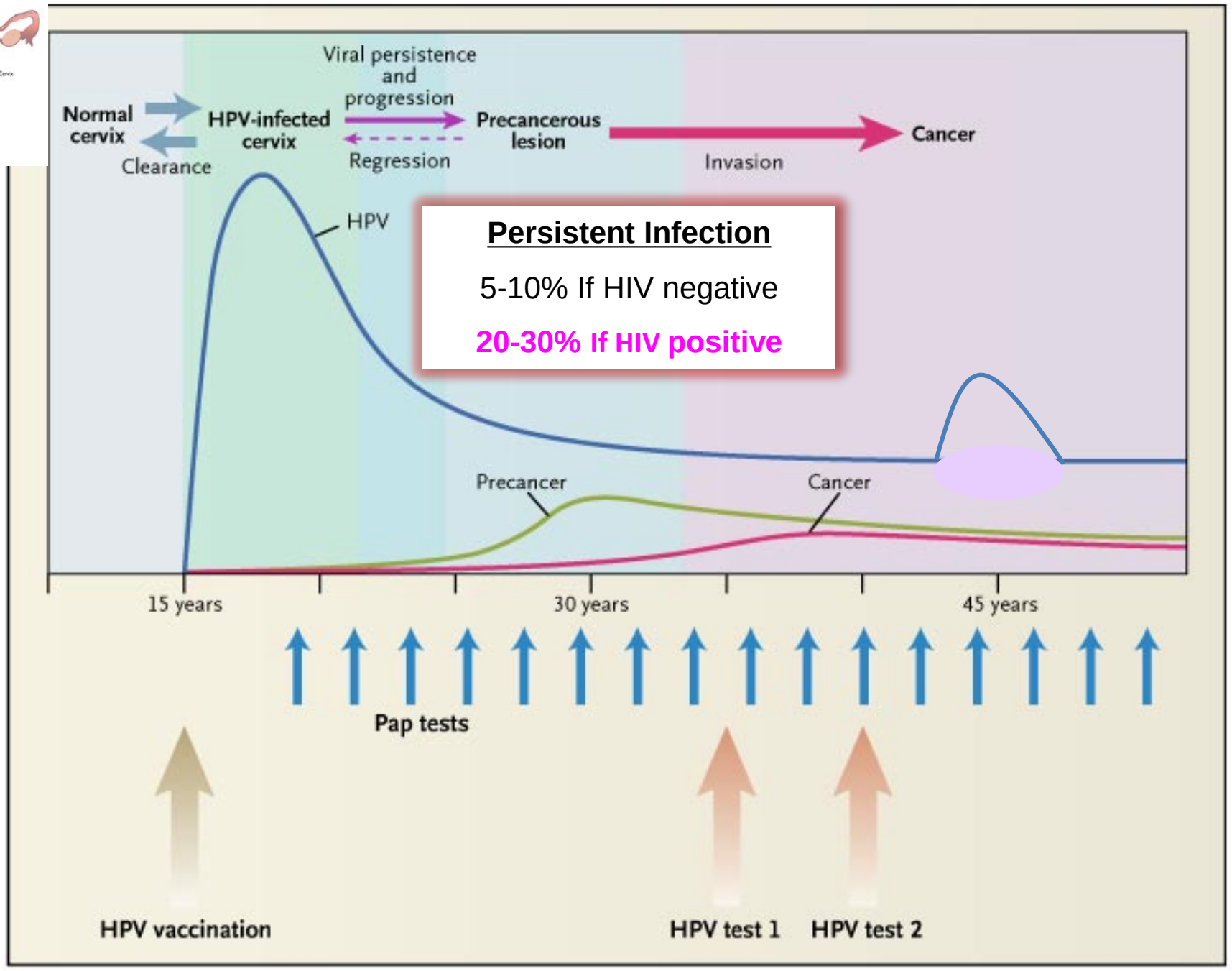
- Many antiretroviral agents are substrates and/or inhibitors or inducers of cytochrome P450 system (CYP)
  - Many anti-neoplastic drugs also metabolized by CYP system leading to either drug accumulation and possible toxicity or decreased efficacy

Safety & Efficacy of Immune Checkpoint Inhibitors in HIV patients

- JAMA July 2019 – 11 case reports, 2 case series
- 73 patients
- Anti Programmed Cell death (Anti PD1): n=62
- Anti- cytotoxic T-lymphocyte Antigen (anti-CTLA-4): n=6
- Anti PD1 + anti-CTLA-4: n=5
- Generally well tolerated (Gr>=3: 8,6%).
- Viral suppression maintained in 93%
- Slight CD4 increase
- Response rates: NSC lung cancer 30%, melanoma 27%, KS 63%

HPV and cancer in HIV patients

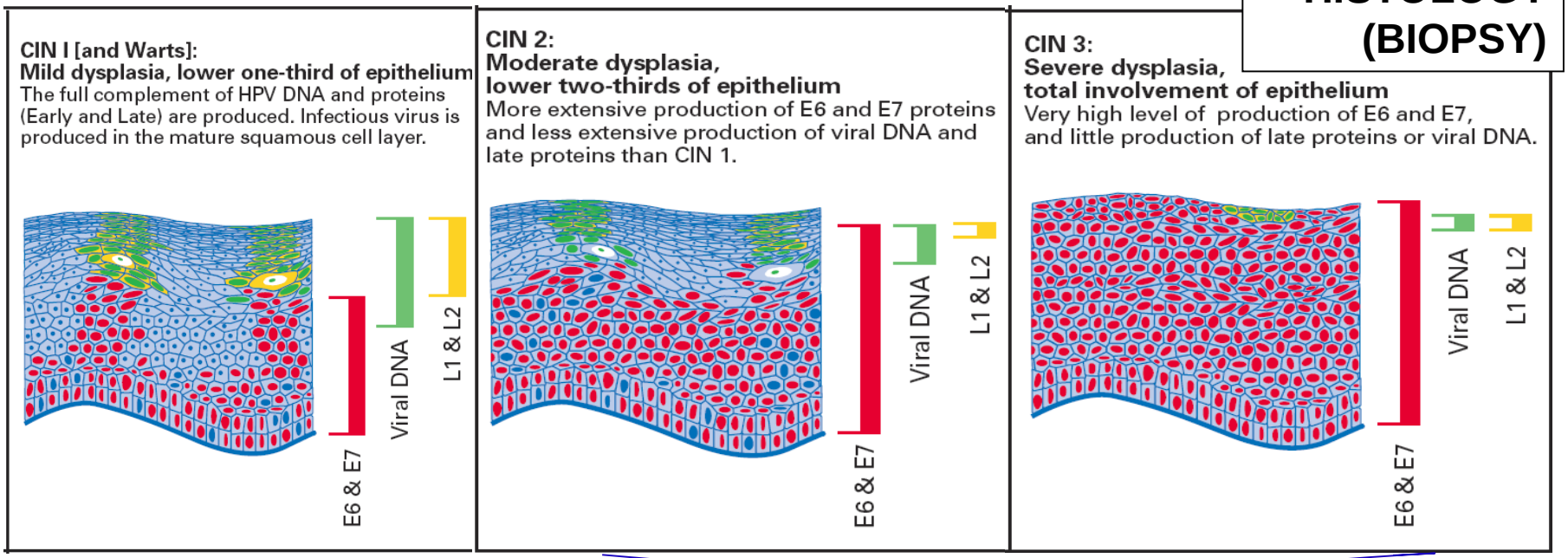




Schiffman, M. et al. N Engl J Med 2005;353:2101-2104

Cervical Intraepithelial Neoplasia

HISTOLOGY (BIOPSY)



LG-SIL Squamous Intraepithelial Lesions **HG- SIL**

CYTOLOGY (Smear)

HPV-induced cancers

- Cervix
- Anus
- Vagina
- Vulva
- Penis

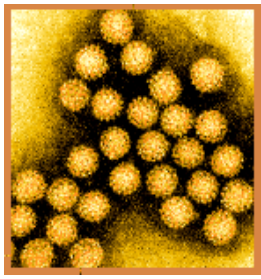
- Oro-pharyngal

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

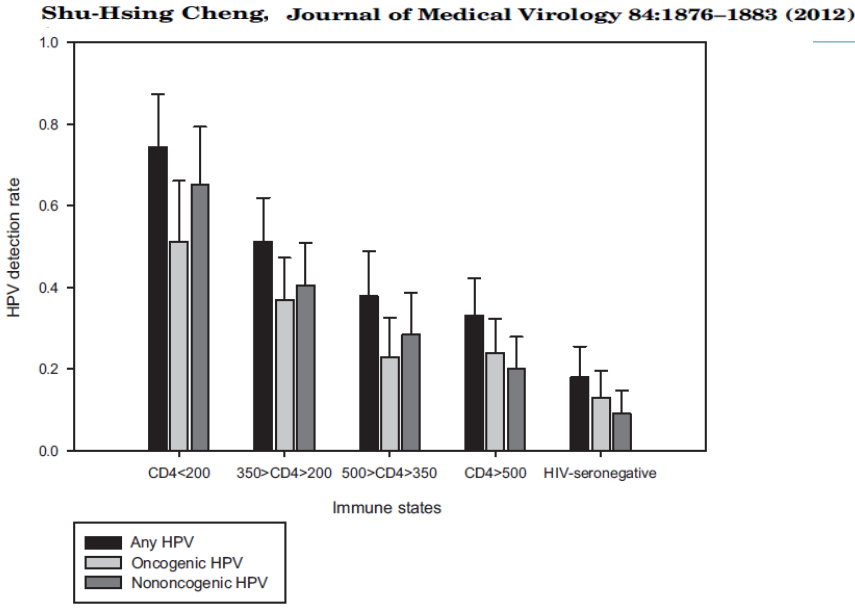
- **Prevalence HGAIN**
  - **43-52%**
  - **In Belgium 25%** (Libois A. EACS 2013)
  - **Risk increases with age**
    - **40-49 years OR 3.09**
    - **>50 OR 4.78**

    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?

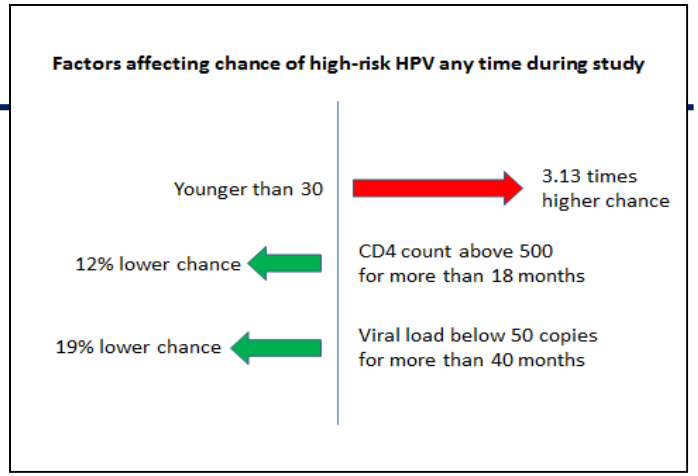
…more recently

FEMALE

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

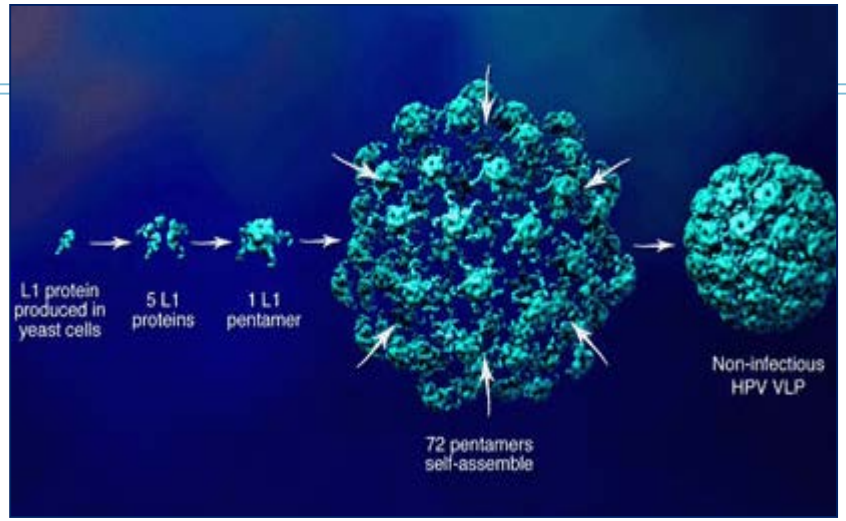
Sustained viral suppression and higher CD4 T cell reduces the risk of persistent HRHPV and of cytological abnormalities

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

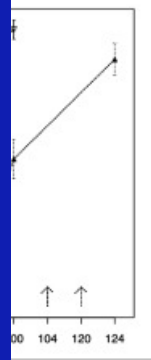
Levin. *J AIDS.* 2010
Wilkin. *JID* 2010
Kahn J. XIX International AIDS Conference. Washington 2012. WEAB0202
WEAB0203

Studies on clinical efficacy ?

Phase IV 2010-2015:
Thailand, Brazil, USA

Gardasil vs Cervarix
in women 15-25 years

ongoing



- ***G***
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e. 2013

Bival

- ***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**