MALIGNANCIES IN HIV

Prof. S. DE WIT
Saint-Pierre University Hospital
Brussels, Belgium

Disclosure

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

Outline

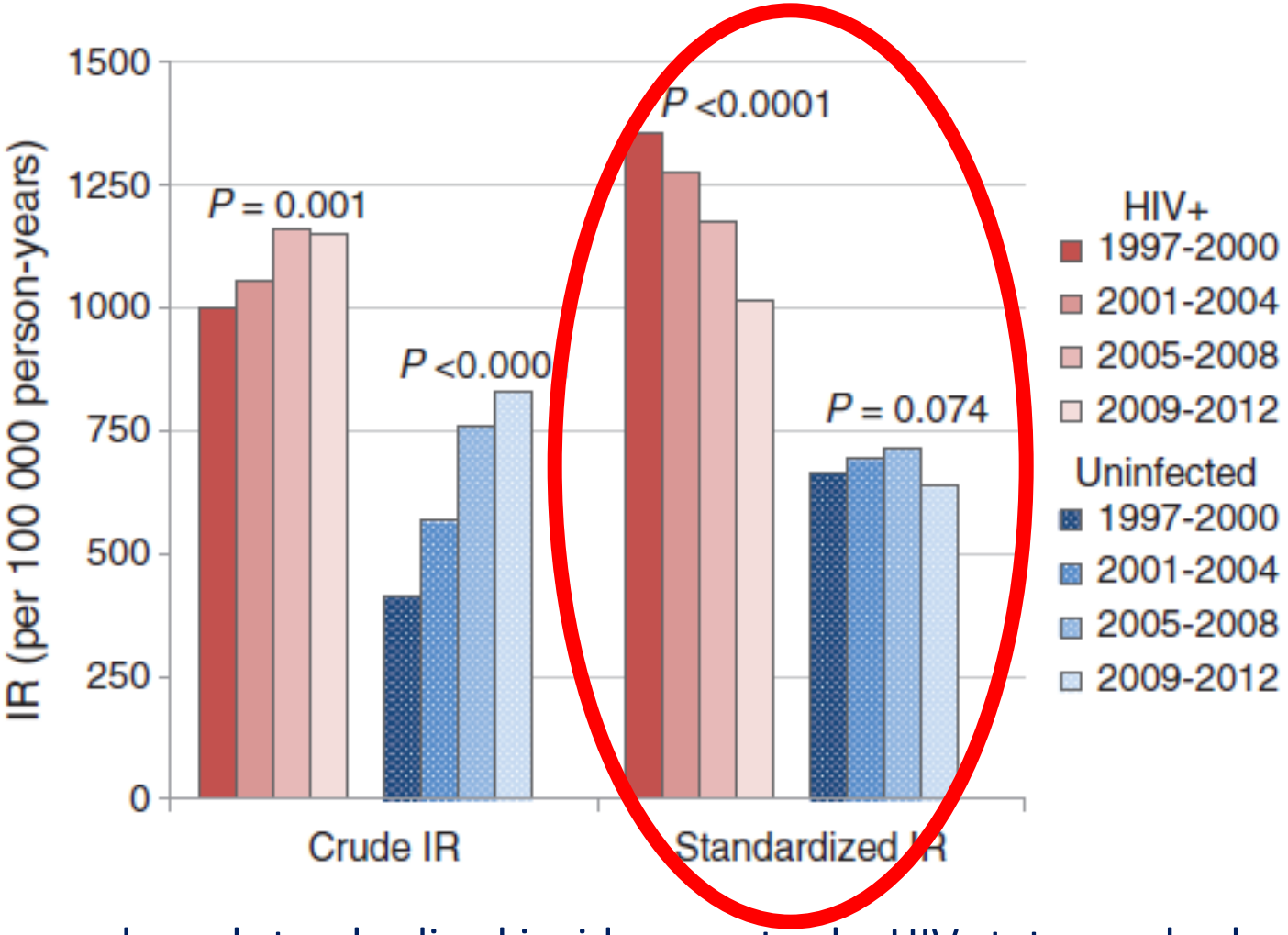
- General consideration on HIV & cancer
- Hepatocellular carcinoma
- Lung cancer
- Breast cancer
- Colorectal cancer
- Chemotherapy and HAART
- HPV and cancer

HIV and cancer

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

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

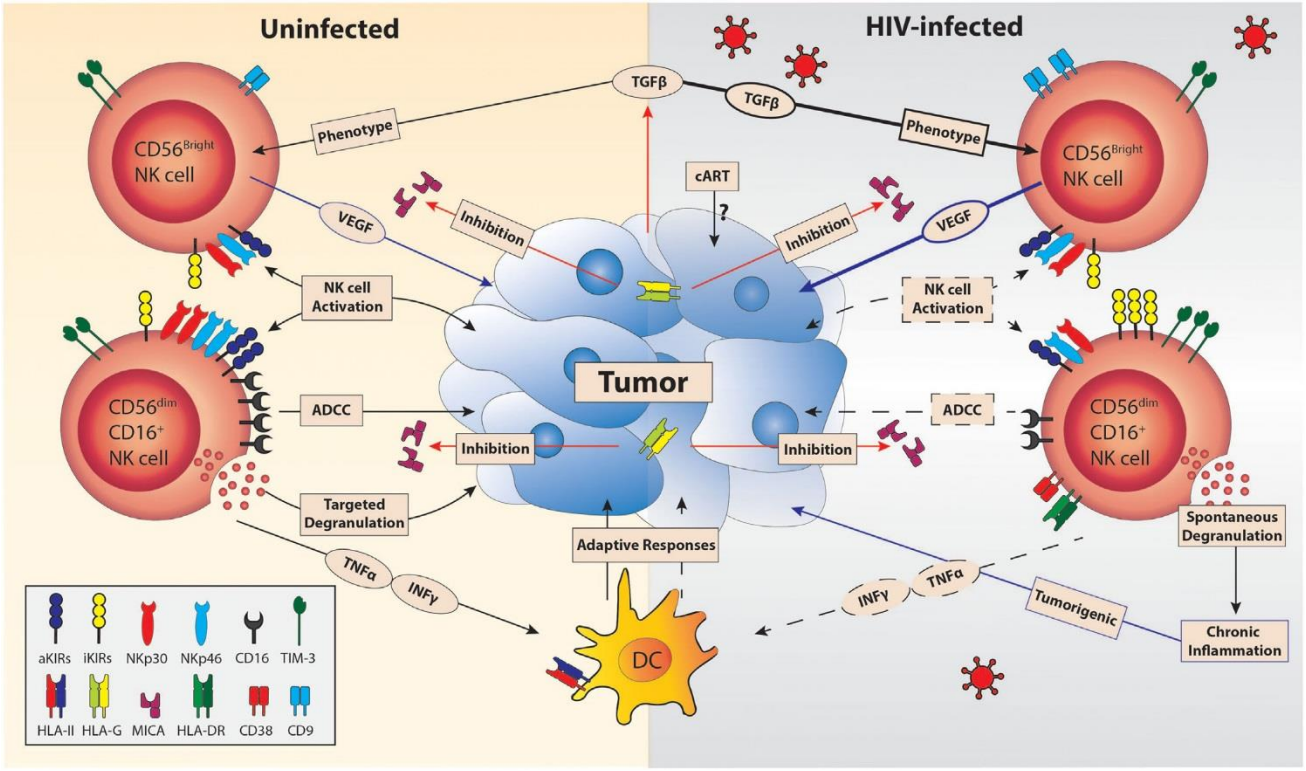
Most important risk factors for NADC

- Increasing age
- Smoking
- Co-infection with oncogenic viruses:
  - Epstein Barr
  - HPV
  - HHV8
  - HBC
  - HCV

Others risk factors for NADC

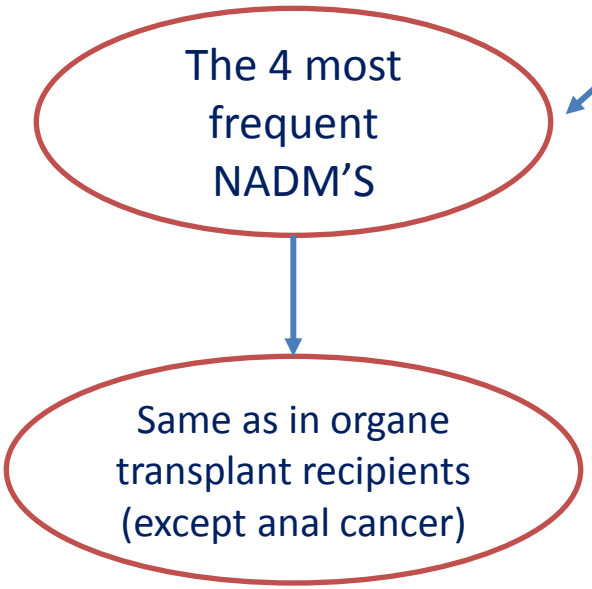
- Length of time since HIV diagnosis /lower nadir CD4
- Irreversible and persistent disruption and damage in lymphoïd tissues, despite effective viral suppression and improved levels of circulating CD4
- Role of ART remains controversial (anal cancer, Hodgkin's lymphoma?)

Role of Natural Killer Cells in HIV-Associated Malignancies



Non AIDS malignancies

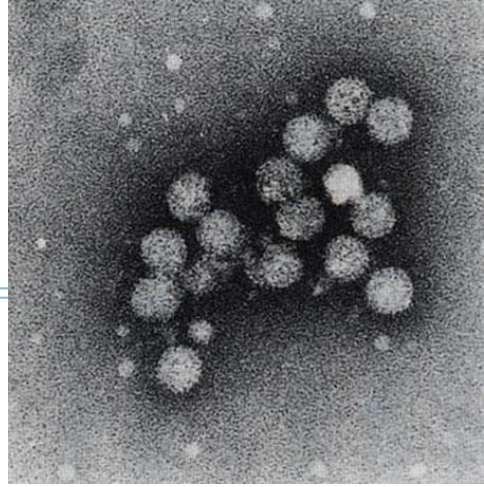
- 34 % of causes of death in France in the cART era
- Relative risk highly variable:



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%

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

- 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 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 : 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)

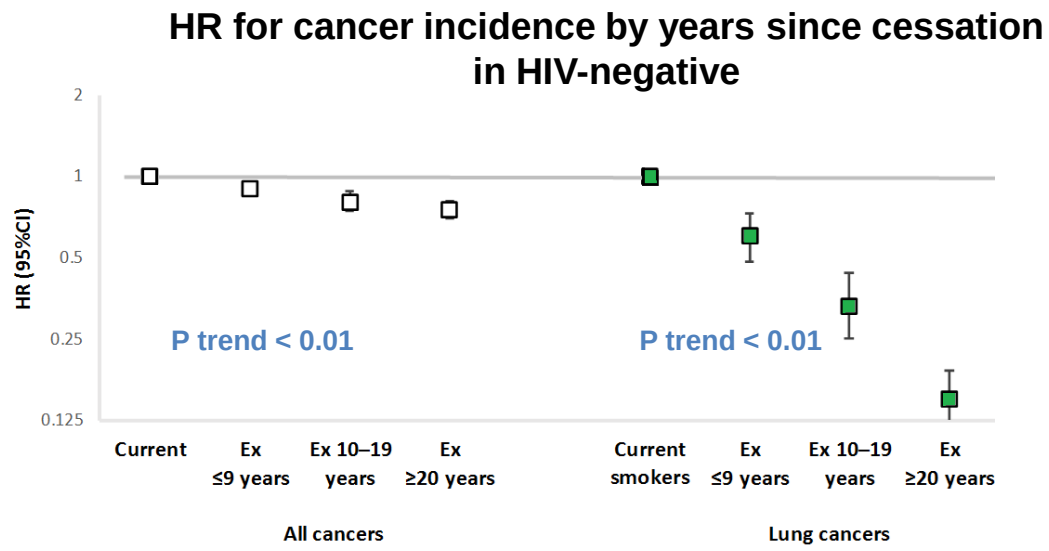
Smoking cessation in HIV patients

- 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

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

Smoking cessation in the general population

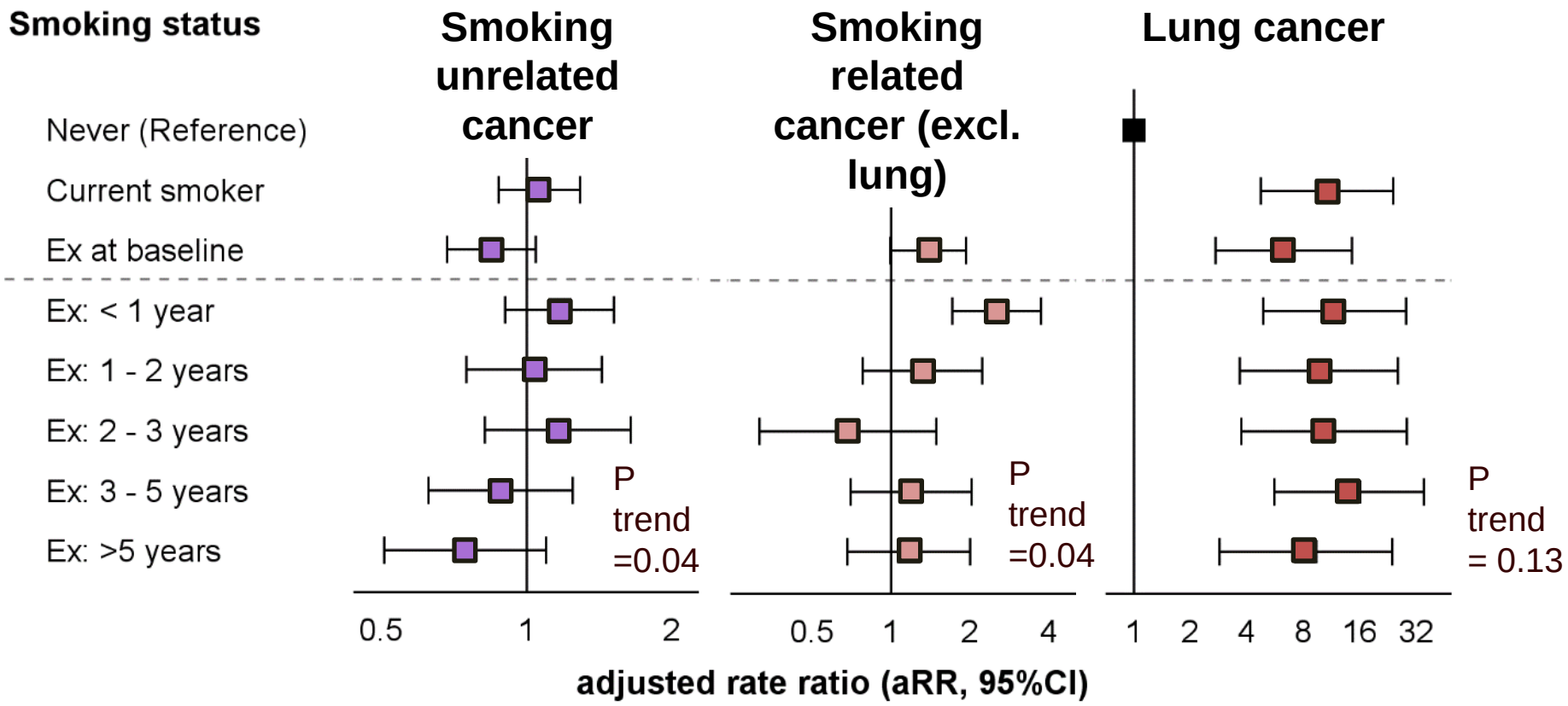
- The decline in cancer incidence with longer time since cessation is well established in the general population
- Reduction in incidence varies by cancer type
- Lung cancer risk is halved after 10 years of cessation



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

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

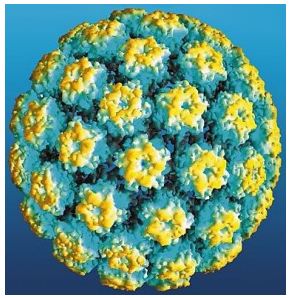
- **UDP Glucuronosyltransferase 1** metabolizes several ARV's such as PI's and maraviroc and antineoplastic drugs such as irinotecan and etoposide

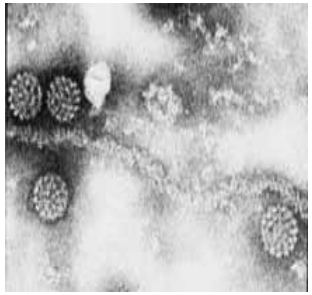
- **P-glycoprotein efflux pump (or MDR1 or ABCB1)** plays a vital role in absorption and cellular transfert of PI's and cytotoxics such as vinca alkaloids, taxanes, doxorubicin and etoposide

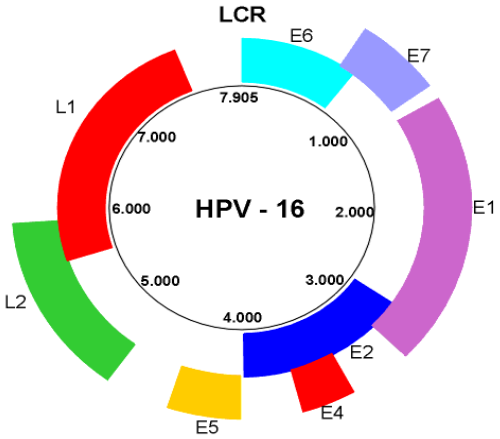
- Expression of CYP 450, UDP-G1 and Pgp is determined by numerous genetic polymorphisms

HPV and cancer in HIV patients

HPV: Human PapillomaVirus







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 **16**

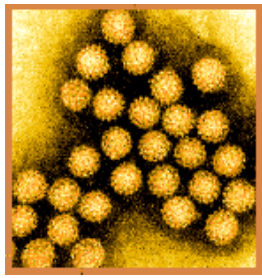
Cervical cancer **16, 18,** 31, 33, 35, 39, 45, **51, 52,** 56, 58, 59, 68

70%

90%

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

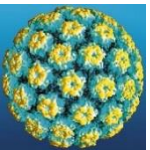
Tugizov. Virology 2013

  - Clinical level

The burden of HPV infections and induced lesions in HIV + 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 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

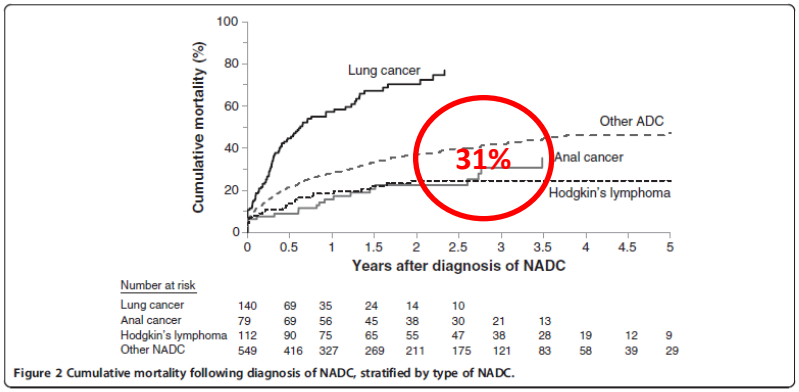


Figure 2 Cumulative mortality following diagnosis of NADC, stratified by type of NADC.

French Hospital Data-ARNS CO4 Cohort : 100,000 patients followed from 1992 to 2009: Survival at 5 years (2005-2009): 63% Hleyet M. *International Journal of Cancer* 2015

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**?

Minkoff . JID 2010	n= 286	30 months	**Decrease HPV prevalence from 22 to 14%, Decrease SIL incidence and prevalence**
Konopnicki D. JID 2013	n= 652	61 months	**Undetectable HIVRNA for > 40 months or CD4>350-500 > 18 months Decreases the risk of persistent HR HPV**
Adler D. AIDS 2012	n= 1123	66 months	**Decreases SIL incidence Increases SIL regression**
Blitz S. JID 2013	n=750	24 months	**Decreases HR HPV prevalence Increases SIL regression**
Zeier M. AIDS 2015	n=300	22 months	**Each month on cART decreases the risk of: any HPV 9% (0.89-0.94) HPV16 50% (0.37-0.67)**
Chen Y. AIDS 2014	n= 1360	2000-2008	**cART associated decreases risk of cervical cancer 0.20 (0.05-0.77) & 0.01 (0.00-0.47) if 85% adherence and >3 years of cART**
Konopnicki D.	n= 766	41 months	**Undetectable HIVRNA for > 37 months or CD4>350-500 > 17 months decreases risk of SIL**

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.*

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

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

Decreased HPV and AIN if cART

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

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

American veterans cohort: retrospective analysis, n= 45.000, 377 with anal cancer, 1985-2009
Chiao E. *J Acquir Immune Def Syndr* 2013.

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

Retrospective study n=1654 preHAART (<1996) & postHAART (1996-2008).
Duncan K. *AIDS* 2015

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

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

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

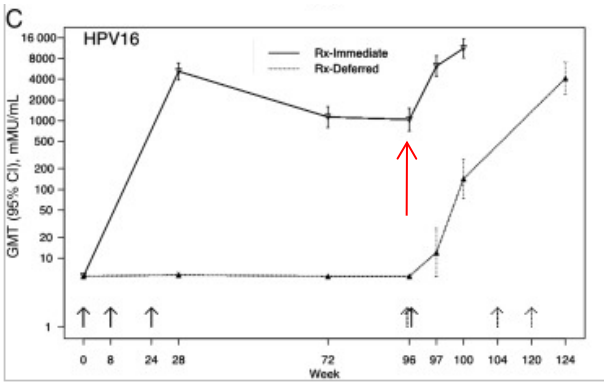
Prophylactic Vaccine

	Bivalent (2vHPV)	Quadrivalent (4vHPV)	Ninevalent (9vHPV)
			
	Cervarix®GSK	**Gardasil**®Merck	**Gardasil9**®Merck
HPV Genotypes	16/18	16/18 + 6/11	16/18/31/33/45/52/58 + 6/11
Adjuvant	ASO4 monophosphoryl lipid A = detoxified derivative of LPS of Salmonella adsorbed on aluminium	Aluminium	Aluminium
FDA/EMA approval	2007	2006	2014/15
	Females and males	Females and males	Females and males
Indication: prevention of	▪Precancerous lesions and cancer in the cervix, vulva or vagina and anus	▪Precancerous lesions and cancer in the cervix, vulva or vagina and anus ▪Genital warts	▪Precancerous lesions and cancer in the cervix, vulva or vagina and anus ▪Genital warts
Vaccination dosing	▪0 and 6 months < 15 years ▪0, 1 and 6 months if ≥15 years	▪0 and 6 months < 15 years ▪0, 2 and 6 months if ≥15 years	▪0 and 6 months < 15 years ▪0, 2 and 6 months if ≥15 years

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)

Levin. *J AIDS.* 2010; Weinberg A. *JID* 2012
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?

	PRO	CON
2vHPV	Higher level of antibody: clinical meaning? Longer protection? Less doses? Cross-protection HPV 31/33/45 Kavanagh K. Lancet Infect Dis 2017	No protection against condyloma
4vHPV	Protection against genital warts	•Price •Availibility? •70% of cancer
9vHPV	Largest protection against cancer (90%) and condyloma genotypes	Price

How many doses in HIV+ patients? Guidelines / Recommandations

➢ **EACS**:

Human Papilloma Virus (HPV)	Shared risk with HIV of contracting infection. Higher rate of cervical and anal cancer	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

?Children, adolescents? (2015)

➢ **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