MALIGNANCIES

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HIV and cancer

- AIDS-defining malignancies:
  - Kaposi's sarcoma — **HHV8**
  - Non Hodgkin lymphoma 1985 — **EBV**
  - Cervical cancer 1993 — **HPV**

- Non AIDS-defining malignancies (NADM) is increasing
  - Linked with virus **HPV** (Anal), **HBV** and **HCV** (Liver), **EBV** (HL)
  - Linked with previous immunodeficiency and other factors

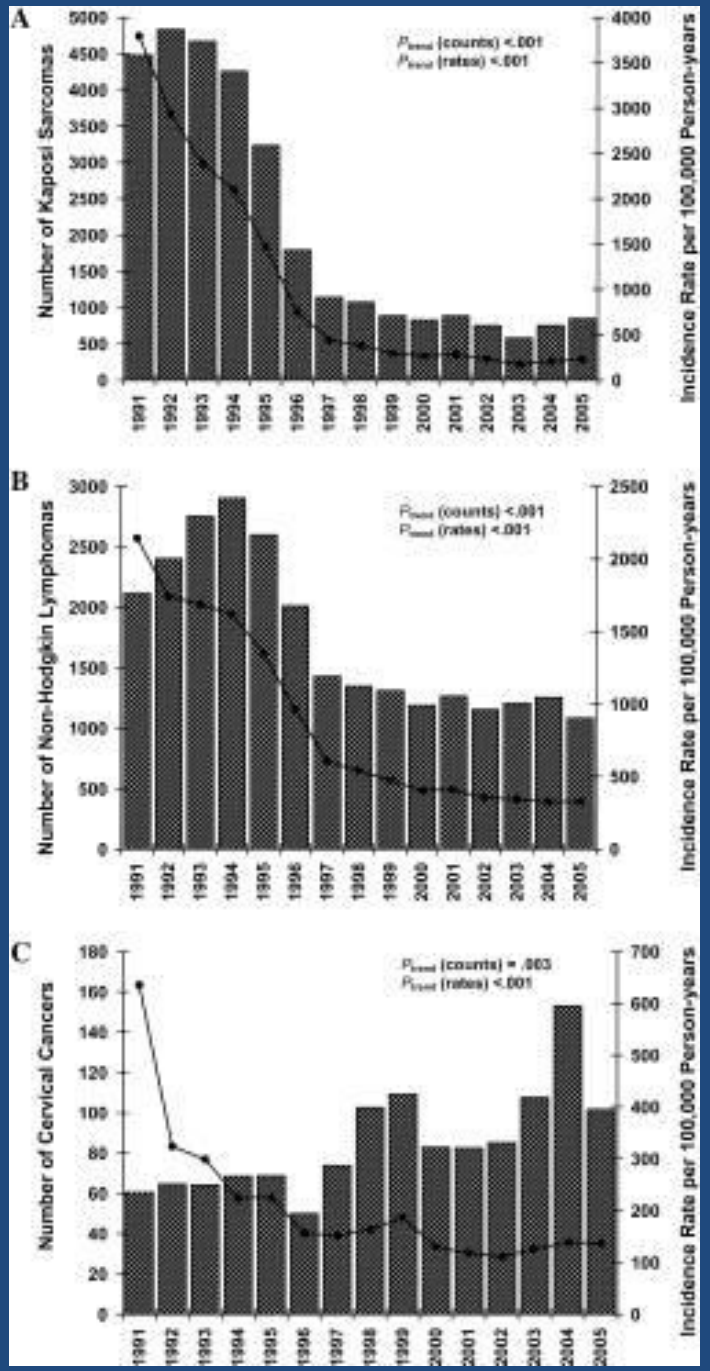
Background

- Before introduction of HAART, ADCs common, including Kaposi's sarcoma, NHL, and invasive cervical carcinoma
- Rate of ADCs significantly increased from early to late pre-HAART era and then significantly decreased following introduction of HAART
- Rates of nADCs stable during pre-HAART eras and then significantly increased following introduction of HAART

SIR = Standardised Incidence Ratio

$$= \frac{\text{Nb cases of cancer in the HIV population}}{\text{Expected nb of cases in the general population, calculated with local cancer registry incidence}}$$

Cancer burden of Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer among people living with AIDS in the United States during 1991–2005.



A) Estimated counts (ie, number of cancers) and standardized incidence rates of Kaposi sarcoma.
B) Estimated counts and standardized incidence rates of non-Hodgkin lymphoma.
C) Estimated counts and standardized incidence rates of cervical cancer among women.

Bars depict the estimated counts and **points connected by lines** depict the incidence rates standardized to the 2000 US AIDS population by age group, race, and sex. Trends in cancer counts and rates were estimated with linear regression. Two-sided *P* values were calculated using the χ^2 test.

Cancer Incidence in AIDS Patients

- Study of cancer risk in AIDS patients from 1980-2006 (N=372,364)
- Predominantly male (79%), non-hispanic black (42%), MSM (42%)
- Median age of 36 years at the onset of AIDS

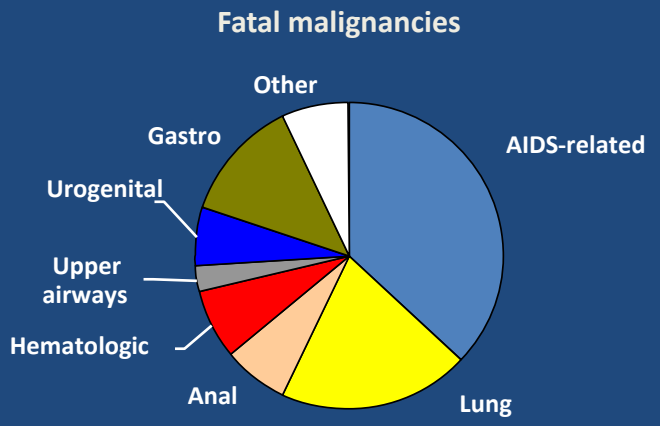
Cancer type	No. cases	SIR	95% CI
AIDS-defining cancers			
Kaposi sarcoma	3136	5321	5137 - 5511
Non-Hodgkin lymphoma	3345	32	31 - 33
Cervical cancer	101	5.6	5.5 - 6.8
Non-AIDS-defining cancers			
Anal cancer	219	27	24 - 31
Liver cancer	86	3.7	3.0 - 4.6
Lung cancer	531	3.0	2.8 - 3.3
Hodgkin lymphoma	184	9.1	7.7 - 11
All non-AIDS related cancers	2155	1.7	1.5 - 1.8

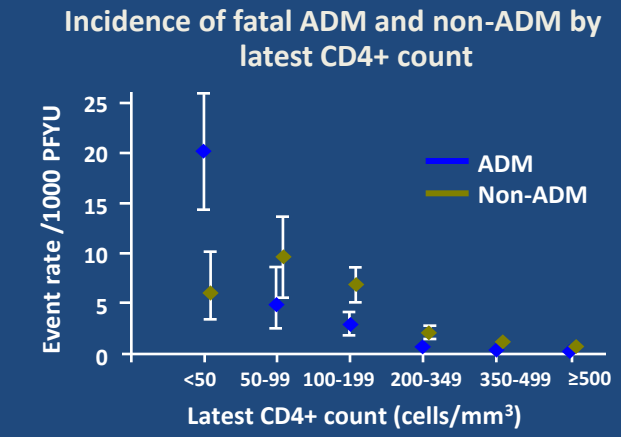
SIR=Standardized Incidence Ratios

Simard E, et al. 17th CROI; San Francisco, CA; February 16-19, 2010. Abst. 27.

D:A:D: HIV and Fatal Malignancies

- Types and risk factors for AIDS-defining malignancies (ADM) and non-ADM studied in D:A:D
  - 23,447 HIV+ patients; 104,691 person-years of F/U
- Fatal non-ADM have become more common than ADM
- Incidence of both non-ADM and ADM increases with lower CD4+ cell count but is not affected by HIV RNA
- Current smokers had a 2.92-fold higher risk of fatal non-ADM than those who never smoked (risk for ex-smokers 2.02-fold higher)





D'Arminio Monforte A, *et al*.

Increased rates of nADCs. Why ?

- Aging of the HIV population
- Increasing survival of patients with HIV might be associated with an increase of traditional cancer
- Higher exposure to oncogenic factors (infectious & non-infectious)
- 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 avoiding or reversing immune deficiency might decrease cancer risk

Characteristics of cancer immune control

- CD4 cell count
- CTL function
- NK
- Immune memory Central/effector memory
- Level of immune activation:
  - PD-1, IL-10, Treg
- Immune system on pre-cancerous lesions

Cancers in HIV and transplant patients

- The range of cancers occurring at increased rates is strikingly similar in the two groups
- Mostly those known or suspected to be caused by infective agents
- Impact of immunodeficiency on these cancers

IL6 & cancer

- Increased incidence of cancers in the intermittent treatment arm of SMART, associated with increase in of plasma levels of D-dimers & IL6
- IL6 is an important component of autocrine and paracrine circuits that fuel the growth of solid tumors at all stages.
  (initiation, promotion, progression and dissemination)
- In the general population elevated level of IL6 is associated with increased risk of developing cancers.
- IL6 gene polymorphisms are associated with colorectal , cervical & oral cancer.

Non-AIDS defining cancers

NADCs in HIV+ Patients compared to Cancer in HIV (-) Patients

- Occur at a younger age (?)
- Atypical pathology, higher tumor grade
- Diagnosed at more advanced stage
- More aggressive disease course
- Poorer outcomes
- Higher rate of relapse

Virus-related NADC's

Hodgkin disease

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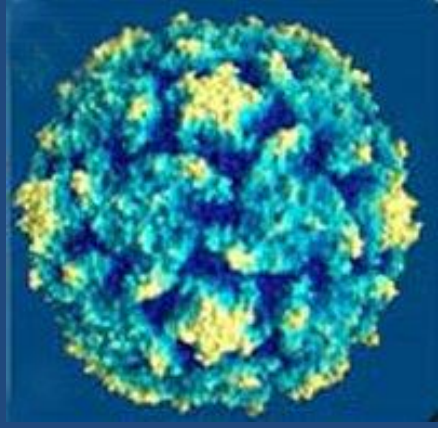
HIV and Hodgkin's Lymphoma



- Due to co-infection with EBV
  - Co-infection rates 75 to 100%, vs 20 to 50% in HIV neg 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

Thompson 2004, Clifford 2005, Herida 2003, Spano 2008

Risk of Hodgkin lymphoma by CD4 count

Table 1. Incidence of Hodgkin lymphoma by CD4⁺ count, adjusted for sex, age, AIDS diagnosis and HIV viral load: French Hospital Database.

Current CD4⁺ count (cells/µl)	Incidence rate per 1000 person years (95% CI)
>500	0.2 (0.1–0.3)
350–499	0.3 (0.2–0.5)
200–349	0.6 (0.4–0.8)
100–199	1.2 (0.8–1.8)
50–99	2.4 (1.5–3.7)
0–49	1.9 (1.1–3.2)

Adapted from data from [42].

Clifford and Franceschi, 2009

Hepatocellular carcinoma

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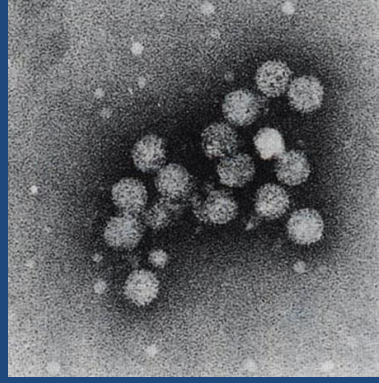
HIV and Liver Cancer



- 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 with transplantation complicated

Murillas 2005, Kramer 2005, Puoti 2004, Hessol 2007

HPV induced cancers

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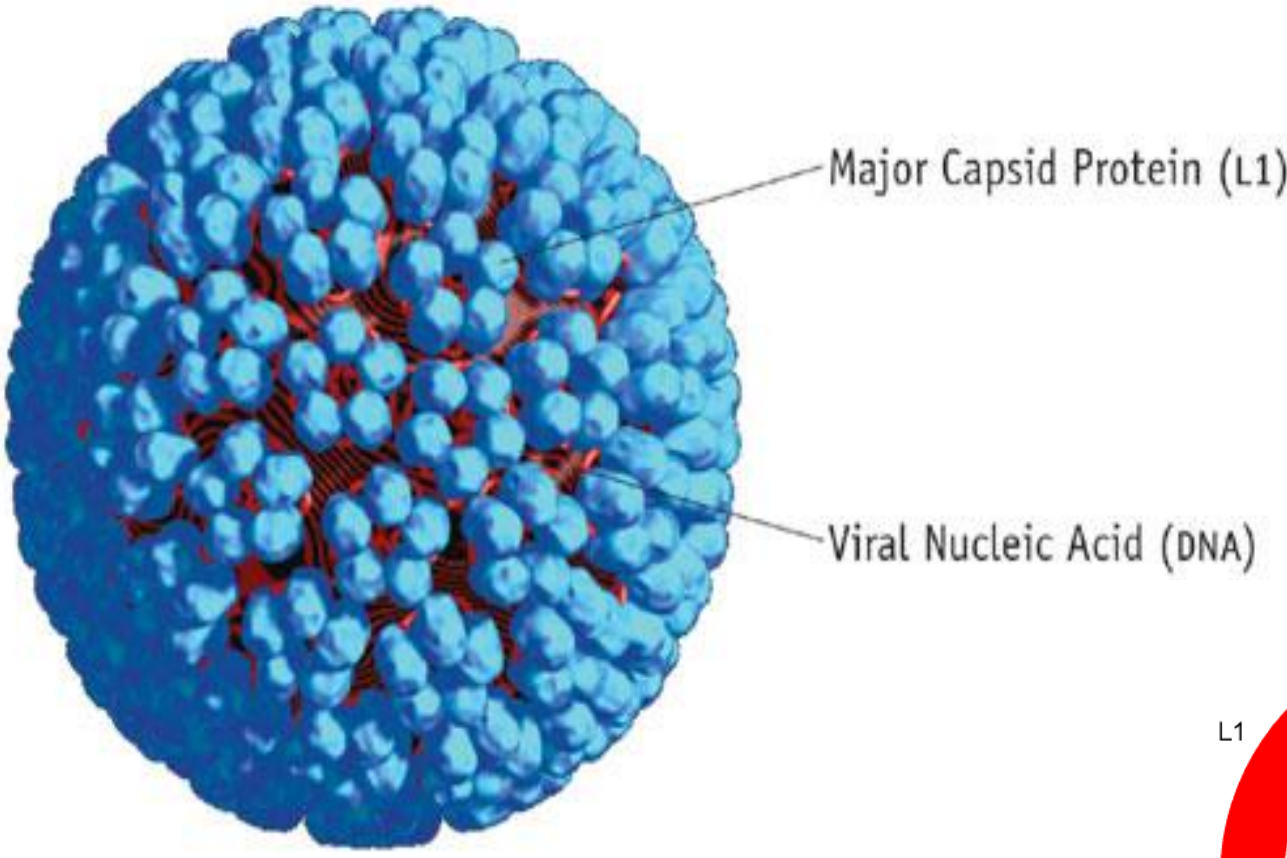
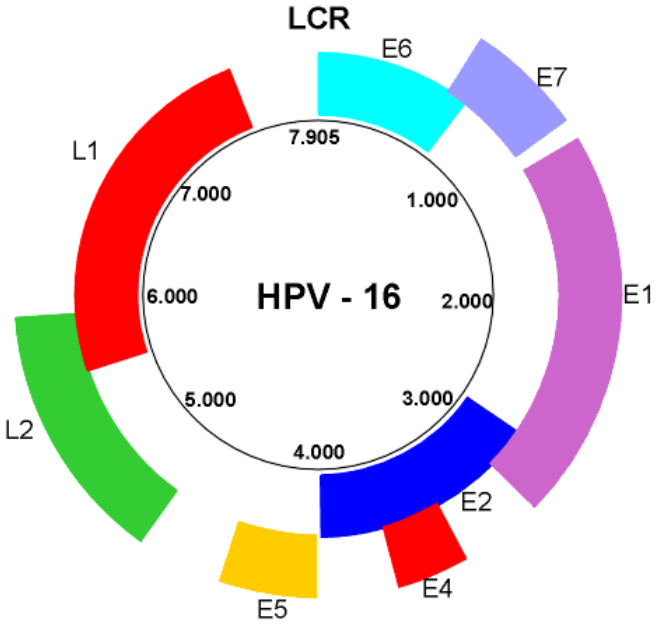
Simard E, et al. 17th CROI; San Francisco, CA; February 16-19, 2010. Abst. 27.

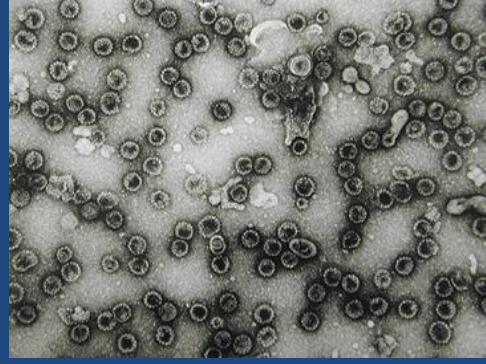
Three-Dimensional Model of Human Papillomavirus



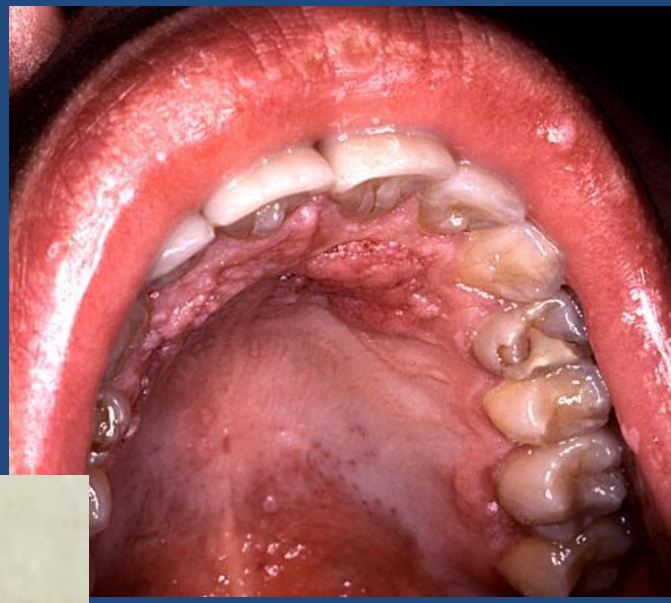
Published in The PRN Notebook, Volume 6, Number 3, September 2001 and The PRN Notebook Onli
Three-dimensional model of HPV created by Louis E. Henderson, Ph.D., Frederick Cancer Rese



100 genotypes infect humans

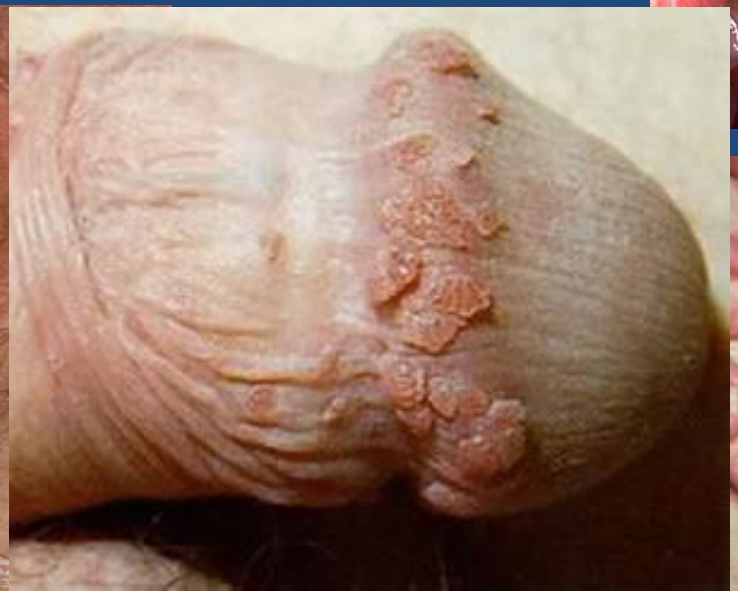


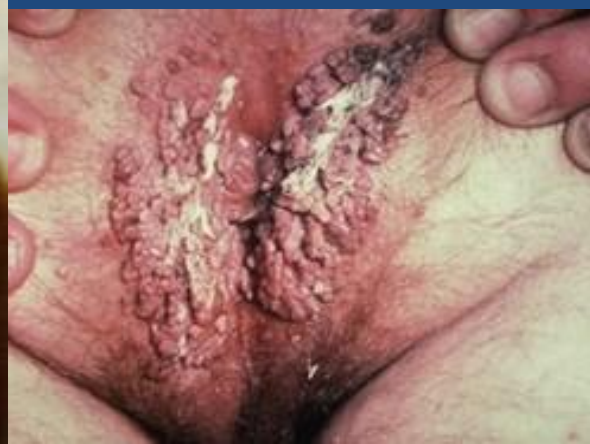
40 genotypes infect genital tract



Low risk HPV genotypes:

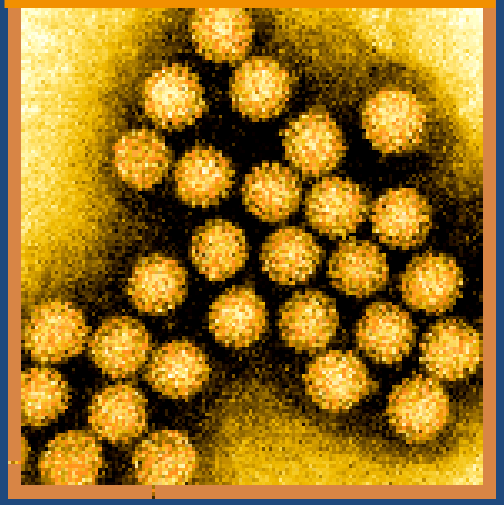
6 and 11 give warts





HPV-induced cancers

	HPV DNA in
• Cervix	99%
• Anus	84%
• Vagina	70%
• Vulva	40%
• Penis	47%



- Oro-pharyngal 35%

70% sk HPV genotypes:

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

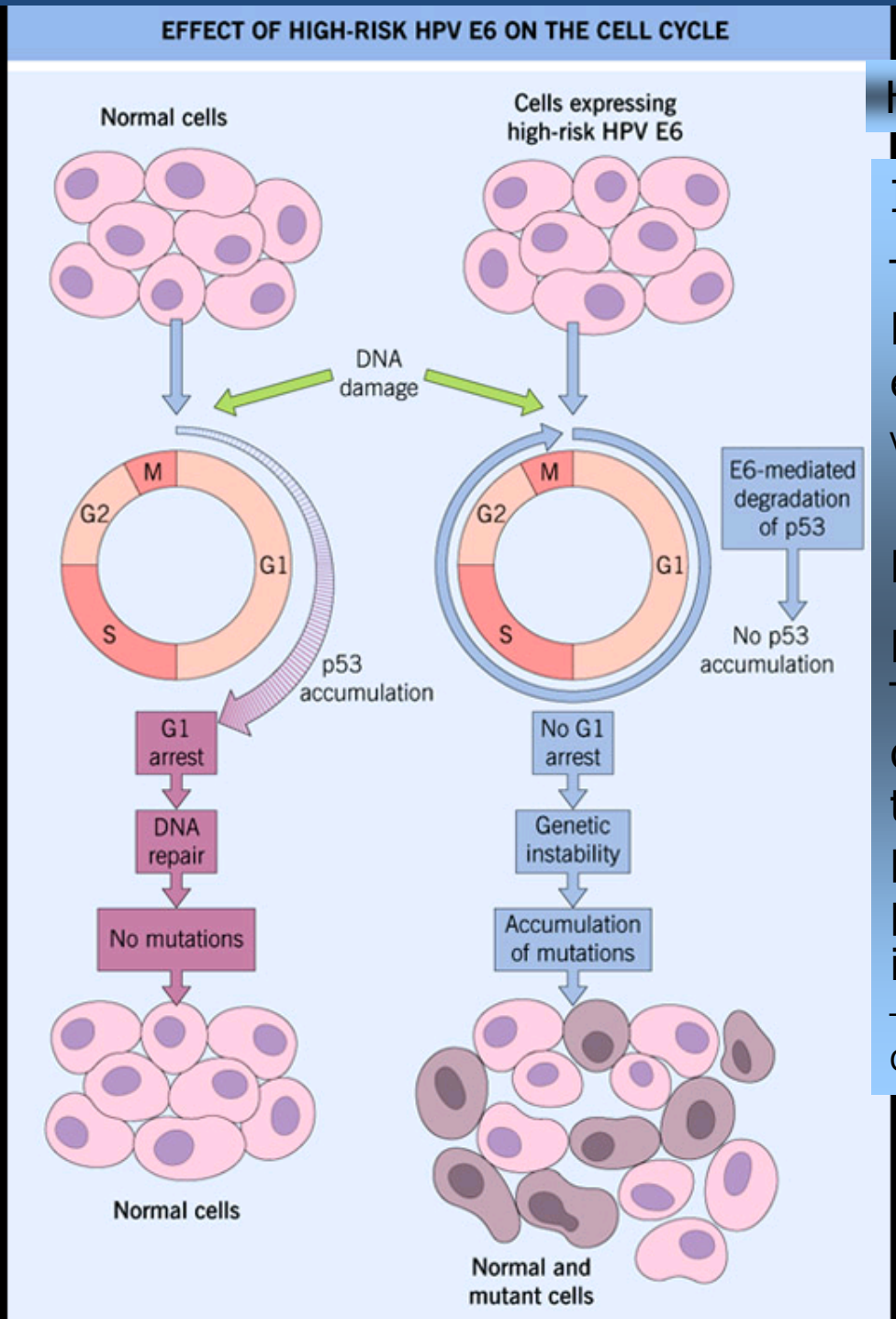
Human defenses against Papillomavirus

- No cell death
- No inflammation
- No ulcer, no exsudate
- No antigen presenting cell

- Transmission by
  - Genital contact
  - Skin contact
  - Self inoculation

- HPV has immune evasion capability

- Weak antibody response in 50-90% of persons



HIV?

In vitro

Tat protein favors HPV E6+7 expression

Vernon. Virus Res 1993

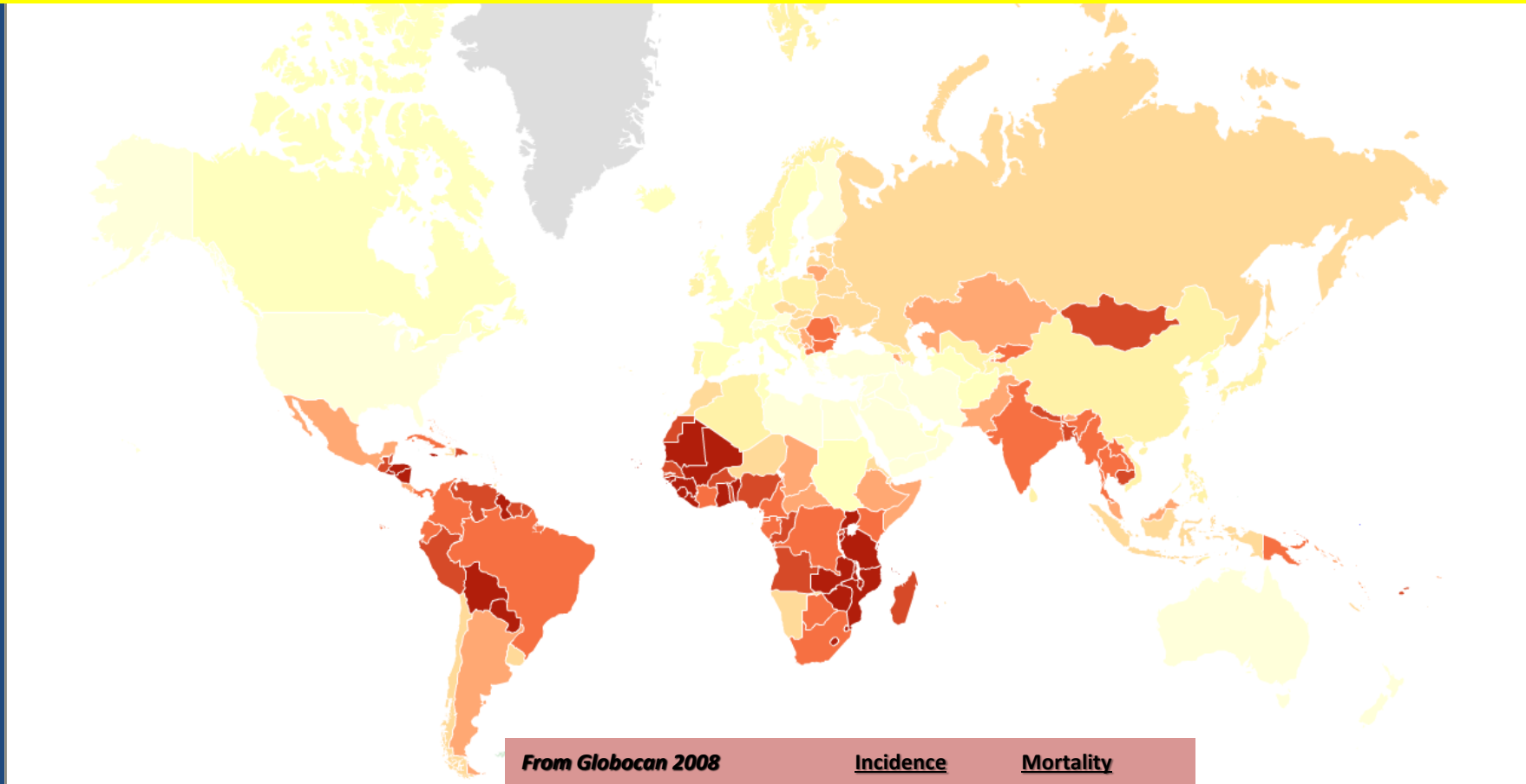
Ex vivo:

HIV tat, gp120, TNF-a and/or IFNg disrupt epithelial tigh junctions and potentiate HPV penetration and infection

Tugizov. XIX Intern. AIDS Conf. Washington 2012

Epidemiology of invasive cervical cancer

per /100,000 women year



0 5.8 12.2 21.0 34.7 57
Age-standardised incidence rates per 100,000

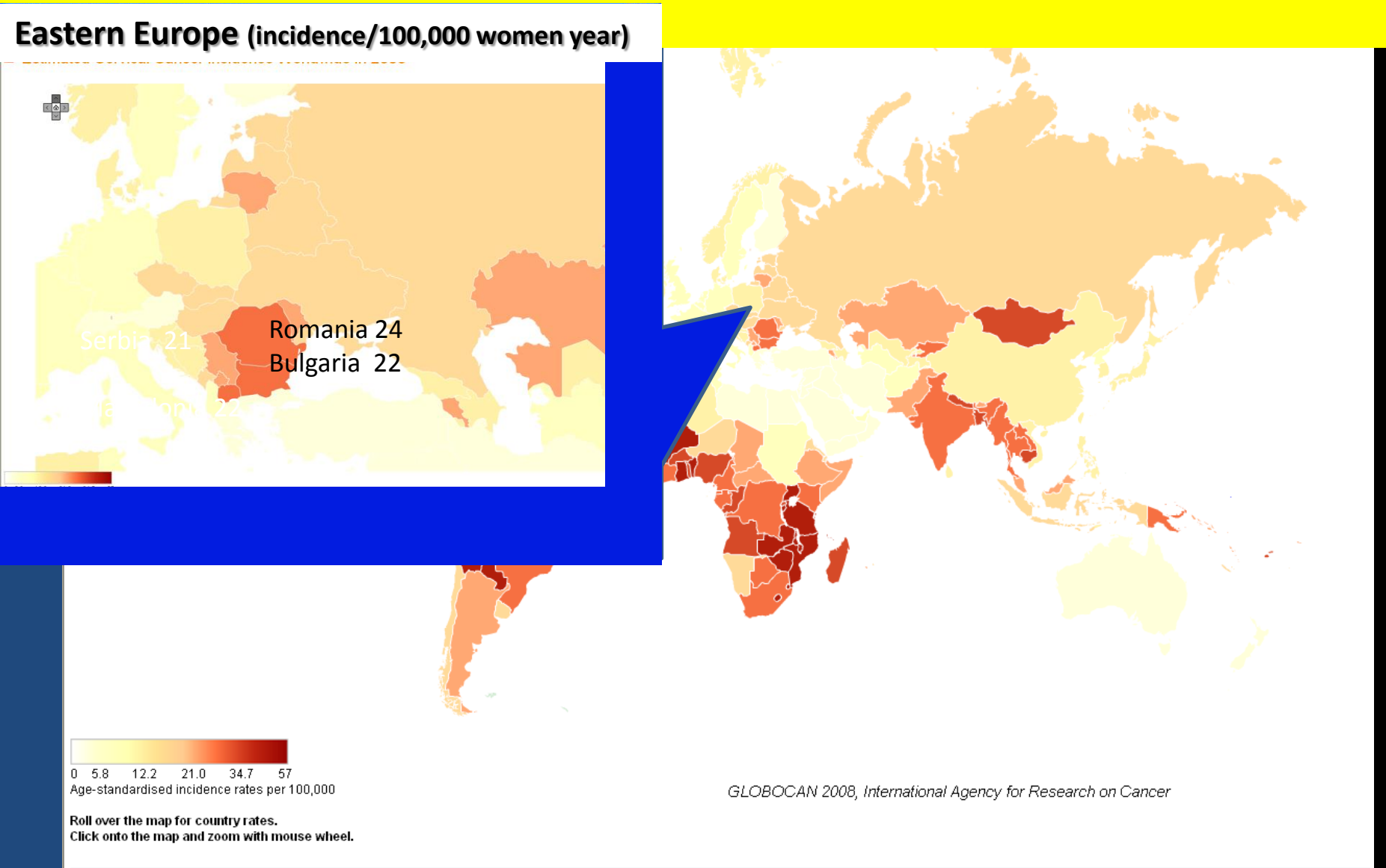
Roll over the map for country rates.
Click onto the map and zoom with mouse wheel.

From Globocan 2008	Incidence	Mortality
	new cases/year	deaths/ year
World	530,000	275,000
Less developed regions	453,000	242,000
More developed regions	76,000	32,000

h on Cancer

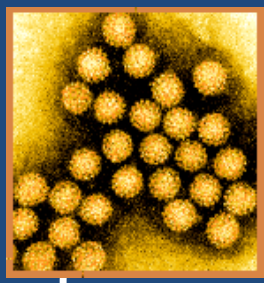
Epidemiology of invasive cervical cancer

per /100,000 women year

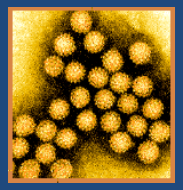


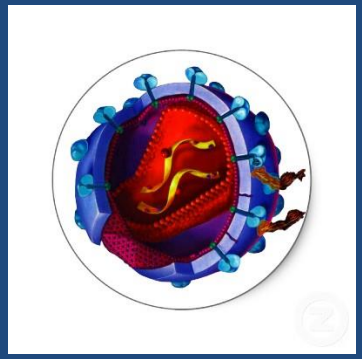
Interactions between HIV & HPV

- Infection with HIV facilitates infection with HPV and HPV-induces lesions



- Infection with HPV facilitates acquisition of HIV
  1. **MSM**
  2. **Women**
  3. **Men (Hetero)**





Infection with oncogenic HPV in HIV women

- Prevalence is higher :**20-40%** (vs.5-10%)
- **Multiple** genotypes: **40 %** (vs. 12%)
- New infection? **Reactivation** of latent infection
- Linked with younger age, lower CD4 and higher HIV VL
- Preventable disease (**Vaccine**)

Palewsky. *J Natl Cancer Inst* 1999

Strickler. *Journal of the National Cancer* 2005

Cancer screening – EACS

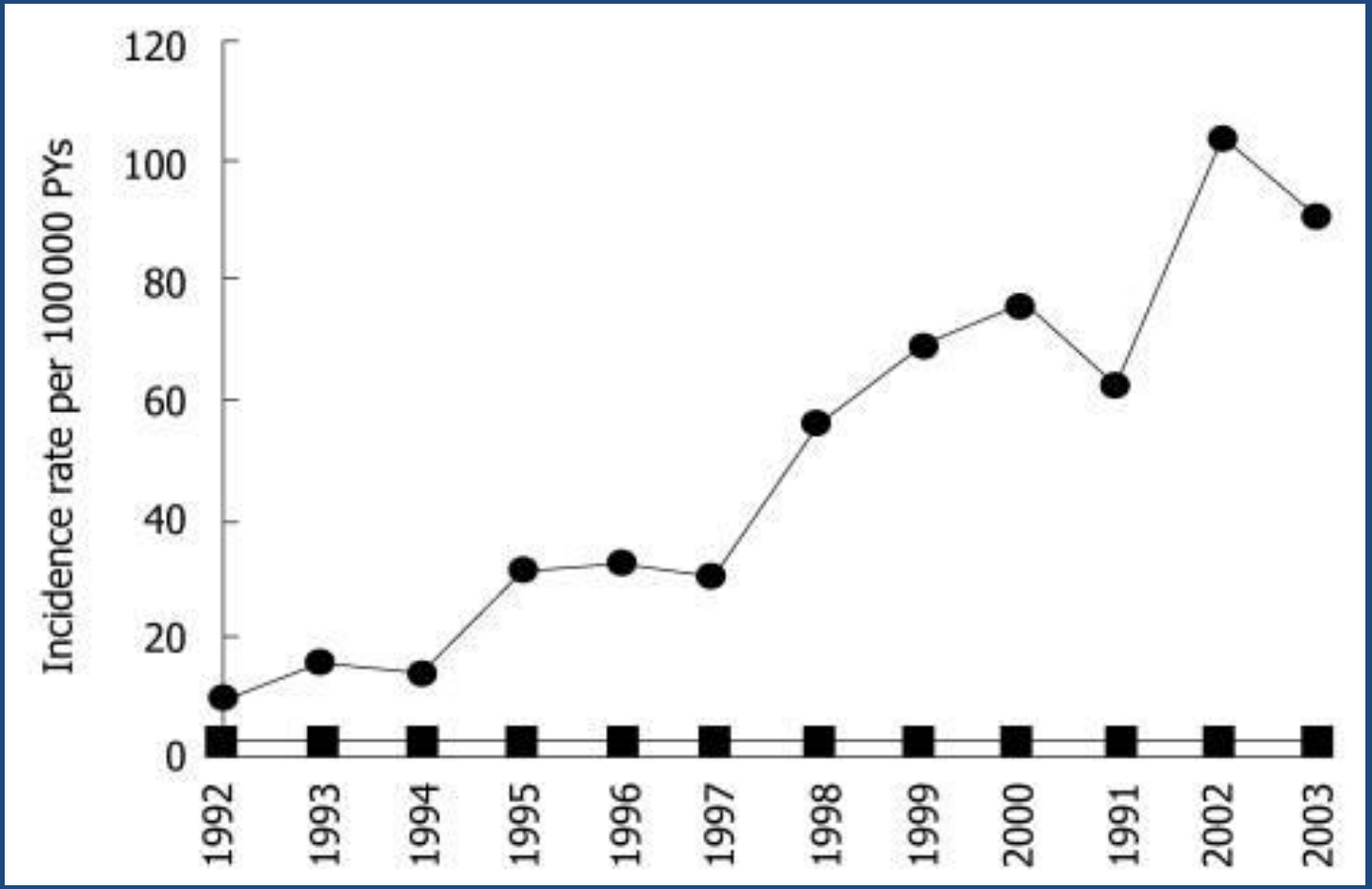
Problem	Patients	Procedure	Evidence of benefits	Screening interval	Additional Comments
Breast cancer	Women 50–70 yrs	Mammography	↓breast cancer mortality	1–3 years	
Cervical cancer	Sexually active women	Papanicolau test, HPV DNA test	↓cervical cancer mortality	1–3 years	Target age group should include at least the age range 30 to 59 years. Longer screening interval if prior screening tests repeatedly negative
Colorectal cancer	Persons 50–75 yrs	Fecal Occult Blood test	↓colorectal cancer mortality	1–3 years	Benefit is marginal

EACS guidelines 2011. Available at http://www.europeanaidsclinicalsociety.org/guidelinespdf/EACS-EuroGuidelines_FullVersion.pdf . Accessed March 2011.

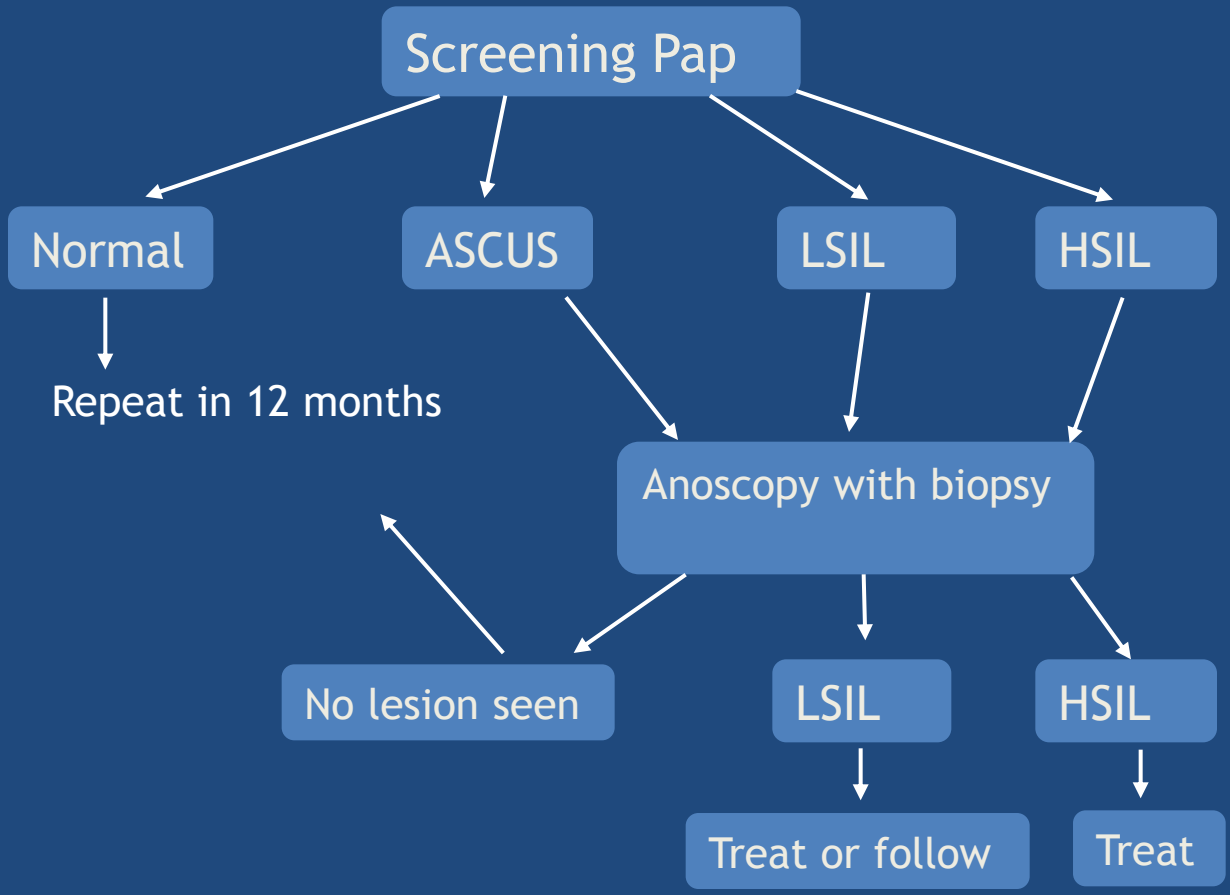
Treatment of cervical lesions in HIV-infected women

- CIN 2+
  - Conisation
  - Follow up biopsies: twice the 1st year
  - *Indication of cART?*
- CIN 1
  - 30% will regress sponteanously
  - Follow up : every 6 months
  - If persistant after 1-2 years or progression : treat
  - *Indication of cART?*

Annual incidence rates of anal cancer among HIV-infected persons (circles) and the general population (squares), USA 1992-2003.



Anal Cytology Screening for AIN in HIV-positive patients



Chin-Hong PV et al. *J Infect Dis.* 2004;90:2070-2076.

Anal cancer screening in HIV+ MSM: Saint-Pierre cohort

353 MSM HIV+

90% Caucasians

Screened by cytology during a one year period

⇩

High resolution anoscopy

- Median age : 44.5 years
- 83% on ARV and viral load (VL)<20 cp/ml : 74%
- Median CD4 632/µl
- Nadir CD4: <200=33% <100=17%
- HIV median follow-up 8 years, Median ARV duration 7 years

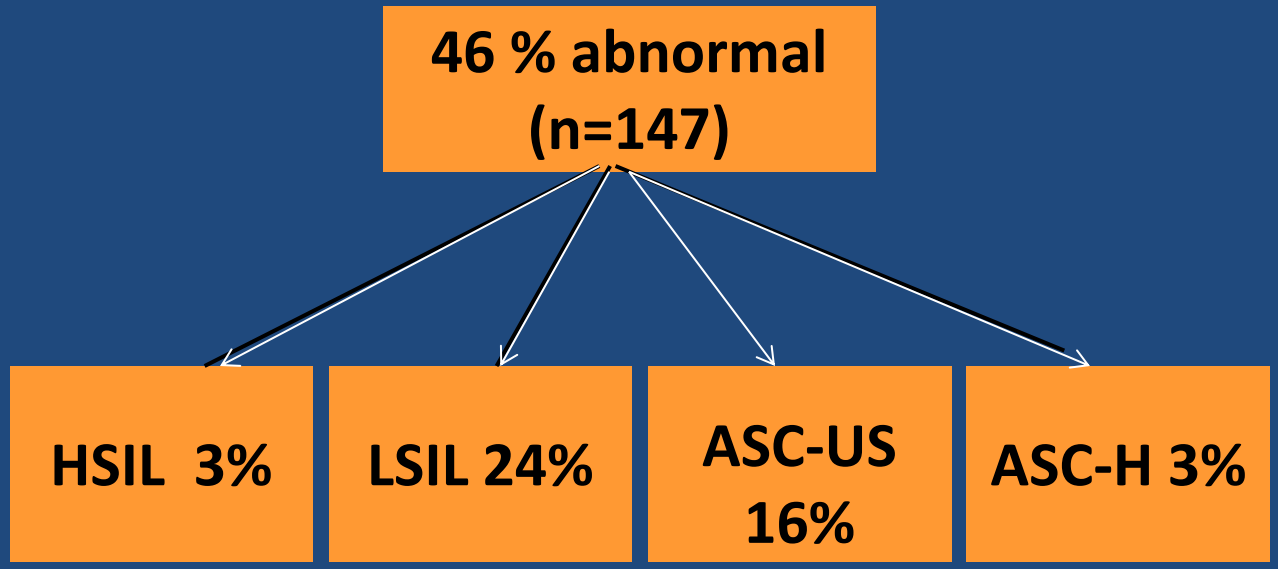
Agnès Libois, F Feoli*, M Nkuize, M Delforge, S De Wit, N Clumeck.
12th HIV drug therapy Conference. Glasgow 2012. Poster 148

Anal cancer screening in HIV+ MSM from Saint-Pierre cohort: Cytology

33 (9.3%) excluded (poor quality) → 320 smears analysed

In patients with normal cytology:

- VL more frequently undetectable (82% vs 64%, p=.0003)
- Median duration of HAART longer (111 vs 61 months, p= .0145)
  - no correlation was found for age, current or nadir CD4



Agnès Libois and al. 12th HIV drug therapy Conference. Glasgow 2012. Poster 148

Oral Cavity and Pharynx Cancer

- Oral cavity and pharynx cancers are uncommon cancers mostly attributable to tobacco and alcohol
- Human papillomavirus (HPV) is an etiologic factor in a subset of oral cavity/pharynx cancers
- Studies suggest HIV-infected individuals have an elevated risk of oral cavity/pharynx cancers
  - HIV-related immunosuppression may promote HPV infection; oral HPV prevalence is higher in HIV-infected individuals
  - HIV-infected might have higher rates of smoking and other behaviours

D'Souza et al., 2007

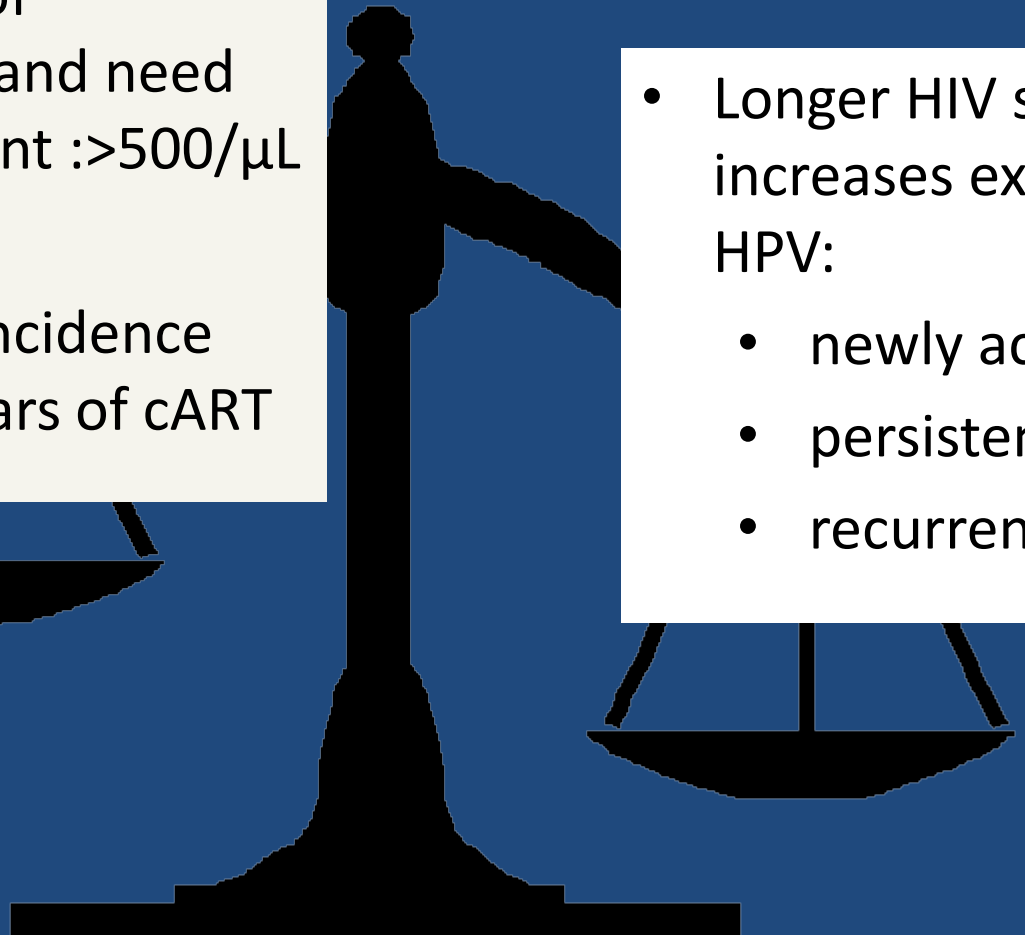
Beachler et al., 2012

In summary

- Screening should be improved for cervical and anal cancer (in both men & women).
- Preventive vaccination against HPV should be more extensively studied and applied in HIV patients
- HPV-induced cancers are not (yet ?) reduced after cART introduction (but may be we need more time…?)

cART impact on HPV infection and induced lesions

- Immune restoration by cART against HPV takes several years (>3 years) of undetectable VL and need high CD4 cell count :>500/µL
- Decreasing AIN incidence might take >4 years of cART



- Longer HIV survival increases exposure to HPV:
  - newly acquired
  - persistent
  - recurrent

Lung cancer

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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 seems probable, 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

Cadranel, Respiration 1999; Bower, AIDS 2004

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

Breast cancer

Breast cancer

- No higher incidence in HIV-positive women

- There might even be a **lower incidence**:
  - Significant decrease was recorded in Tanzania following HIV epidemics. Amir. *J Natl Med Assoc* 2000
  - Significant decrease in relative risk (observed cases/expected cases based incidence in general population). Frisch. *JAMA* 2001

Why breast cancer could be less frequent in HIV women?

- Reduced incidence is also found in other immunosuppressed patients

Steward. *Lancet* 1995

Suggesting that physiological immune response could be a facilitating factor in breast carcinogenesis

- Hormone production is reduced in HIV patients: oestradiol or testosterone

Why breast cancer could be less frequent in HIV women?

- CXCR4-tropic HIV is protective against breast cancer because
  - In vitro: this receptor is highly expressed by tumor cells and CXCR4 HIV induces tumor cells apoptosis

    Endo M. *Curr HIV Res* 2008
  - In vivo : decreased incidence of breast cancer when compared to CCR5 HIV-infected patients

    Hessol N . *PloS ONE Dec* 2010. vol 5;12:e14349.
- Ritonavir has been shown in vitro to reduce breast cancer growth (same for lung & renal cancer)

Breast Cancer

- When occurs:
  - Higher rate of bilateral disease
  - Histology more likely poorly differentiated
  - Early metastasis

Pantanowitz 2003, Gewurz 2005

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Colorectal cancer	Persons 50–75 yrs	Fecal Occult Blood test	↓colorectal cancer mortality	1–3 years	Benefit is marginal

EACS guidelines 2011. Available at http://www.europeanaidsclinicalsociety.org/guidelinespdf/EACS-EuroGuidelines_FullVersion.pdf . Accessed March 2011.

Kidney Cancer

- Incidence rate 2 times higher in HIV+ and 5.8 times higher in patients with AIDS
- Has not gone down during HAART era
- Etiology unclear:
  - Immune deficiency (Immune therapy (IFN, IL) central to treatment)
  - Kidney damage from ART?

Engels 2006, Layman 2008

Colorectal Cancer

- Slightly increased risk in HIV+ pts.

- Higher rates of precursor lesions in HIV+ pts
  - Higher rates of adenomas
  - Larger adenomas (>10mm)
  - Poor histology: villous, high-grade dysplasia

Bini 2006, Yeguez 2003

Prostate cancer

- Conflicting data on SIR: 0.69 – 2
- Low SIR could be due to lack of screening
- HIV+ prostate cancers patients are diagnosed at a similar stage but have reduced survival
- No specific recommendations for screening

HAART and chemotherapy

- Many patients will receive HAART and chemotherapy concurrently with high likelihood of drug interactions
- Protease inhibitors and non-nucleoside reverse transcriptase inhibitors are substrates and potent 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
    - Paclitaxel and docetaxel
    - Vinca alkaloids

Considerations in Treating NADCs with chemotherapy in HIV-positive Patients

- Overlapping Toxicities
- Drug-Drug Interactions
  - Transporters
  - Enzymes (CYP450,etc)

Chemotherapy and HAART Toxicities

- Myelosuppression
  - Zidovudine
- Nephrotoxocity
  - tenofovir, protease inhibitors
- Nausea
  - protease inhibitors, zidovudine,
- Diarrhea
  - lopinavir
- Hepatotoxicity
  - all NNRTIs, all PIs, and all NRTIs

HAART – Chemotherapy Interactions

- Enzymes (CYP450,etc)
  - CYP3A4 especially
- Transporters
  - up-regulated by cancer cells when exposed to chemotherapy, inducing a ‘multi-drug resistance’ phenotype
  - Some ARV’s induce the same mechanisms (P-gp, MRP 1)

Chemotherapy and HAART

Enzyme/ Transporter	HAART Inhibitors	HAART Inducers	Chemotherapy Substrates
CYP3A4	delavirdine, efavirenz, ritonavir, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir	nevirapine, efavirenz	paclitaxel, docetaxel, erlotinib, sunitinib, sorafenib, etoposide, vincristine, vinblastine, vinorelbine, cyclophosphamide
CYP2C9	efavirenz, ritonavir		cyclophosphamide
CYP2C19	efavirenz, amprenavir		cyclophosphamide, ifosfamide, thalidomide
CYP2D6	ritonavir		tamoxifen
CYP2B6	efavirenz, nelfanivir, ritonavir	nevirapine	cyclophosphamide, ifosfamide
CYP2E1	ritonavir		etoposide, dacarbazine
UGT1A1	atazanavir		irinotecan

HAART and Drug Transporters

Drugs	Transporter					
	ABCB1		ABCC1		ABCG2	
	Substrate	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor
NRTI						
Abacavir (ABC)	++		+	+	+++	
Didanosine (DDI)	NT		NT		NT	
Lamivudine (3TC)	+				+	
Stavudine (D4T)			+			
Zalcitabine (ddC)	NT		NT		NT	
Zidovudine (AZT)	+				+	
NtRTI						
Tenofovir disoproxil fumarate	+++		++	+/-	+++	
NNRTI						
Nevirapine						
Efavirenz	+			+		
PI						
Amprenavir				+		
Atazanavir		+		+	+	+
Indinavir				+		
Lopinavir		+		+		+
Nelfinavir	+	+		+	+	+
Ritonavir	+	+		+		+
Saquinavir	++	+		+		+
Tipranavir			+++			

NRTI: Nucleoside analog reverse transcriptase inhibitors. NtRTI: Nucleotide analog reverse transcriptase inhibitors.
NNRTI: Non-nucleoside analog reverse transcriptase inhibitors. PI: Protease inhibitors.
+, ++, or +++ : weak, moderate, or strong substrate/inhibitor. NT: Non-toxic, could not be determined.

Drug Transporters and Chemotherapy

Chemotherapy Transporter Substrates		
ABCB1	**ABCC1**	**ABCG2**
Actinomycin D	Etoposide	Mitoxantrone
Doxorubicin	Teniposide	Methotrexate
Daunorubicin	Daunorubicin	Irinotecan
Docetaxel	Doxorubicin	Topotecan
Paclitaxel	Epirubicin	Imatinib
Epirubicin	Melphalan	Erlotinib
Idarubicin	Vincristine	Gefitinib
Vinblastine	Vinblastine	
Vincristine		
Etoposide		

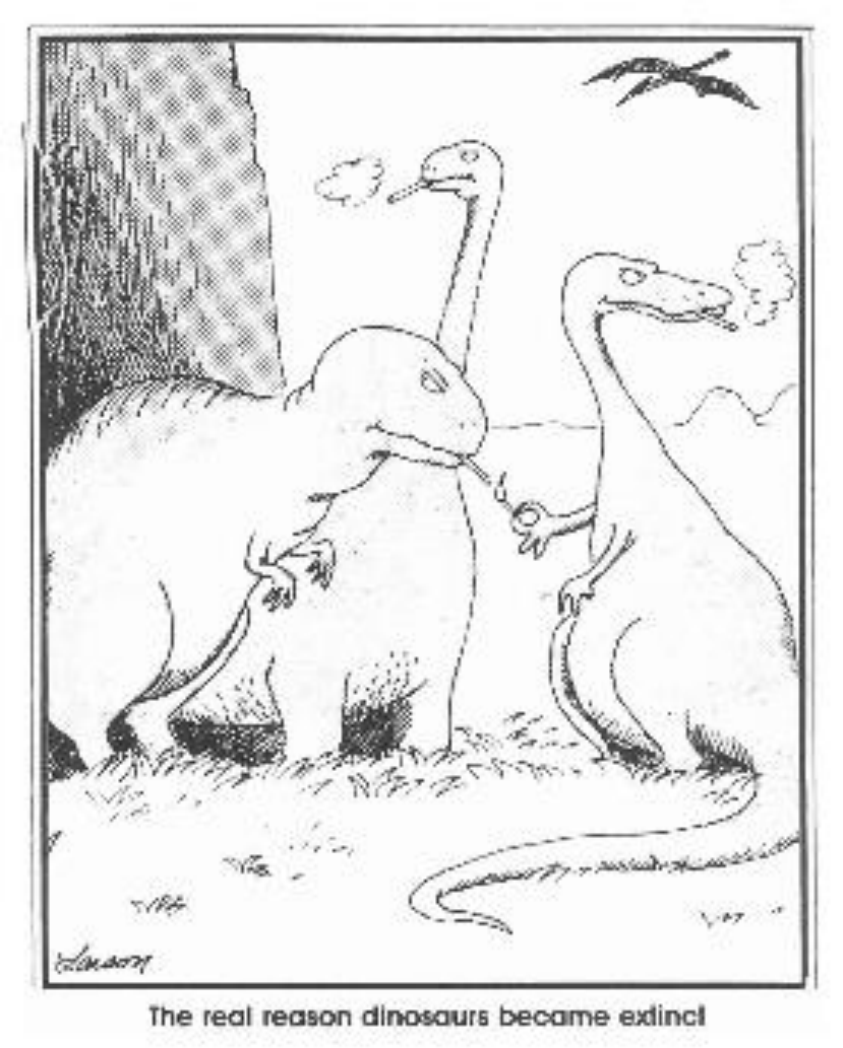
Summary

- Since introduction of HAART, NHL and KS incidence has decreased

- Incidence of other cancers has increased mainly in relation with:
  - smoking
  - viral coinfections,
  - immunosuppression

Summary

- Treatment of HIV-cancer without treatment of HIV rarely works
- Treatment strategies similar for non-HIV infected individuals
- Stigma surrounding HIV infection may prevent accurate diagnosis and treatment.
- Prevention via risk factor control , vaccination and screening



Thank you