EACS European AIDS Clinical Society

Course/Workshop
21.10.2015, 13:30 – 17:00
Room Madrid

WAVE Workshop - Women Against Viruses in Europe - Promoting the Welfare of HIV-positive Women in Europe

HPV-related cancers and their prevention in women

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ULB UNIVERSITÉ LIBRE DE BRUXELLES

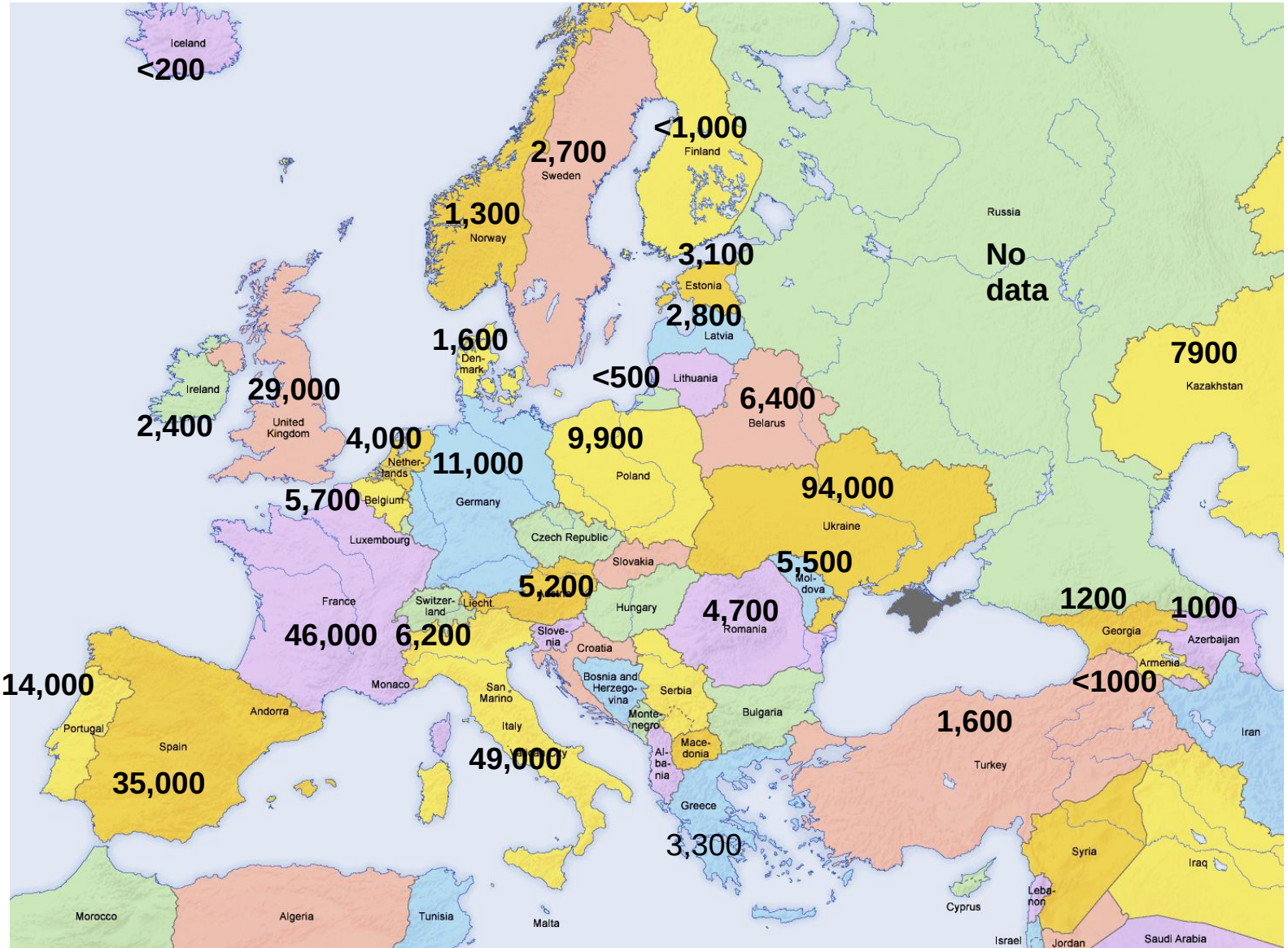
Disclosure

- Presenter: D. Konopnicki
  - Travels and congress Grants from Pfizer, ViiV and MSD.
  - Fee as invited speaker from Janssens.
  - No conflicts of interest.

Women living with HIV according to UNAIDS and ECDC in 2012

400,000 women living with HIV

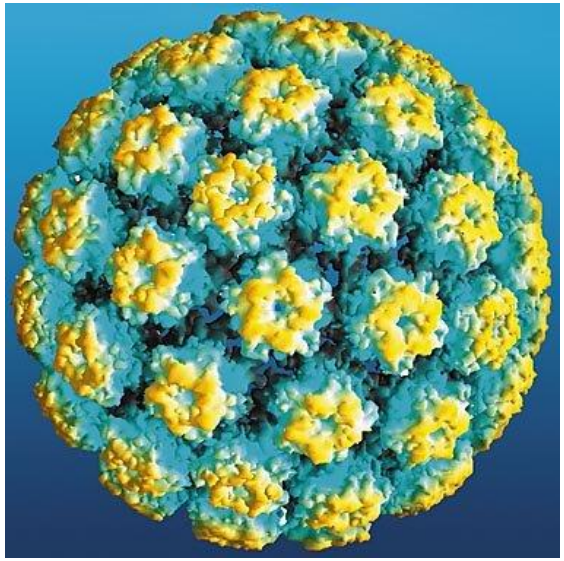
7,500 new diagnosis of HIV in women

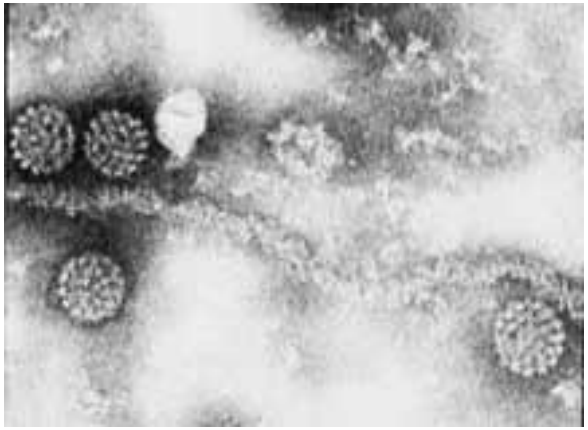


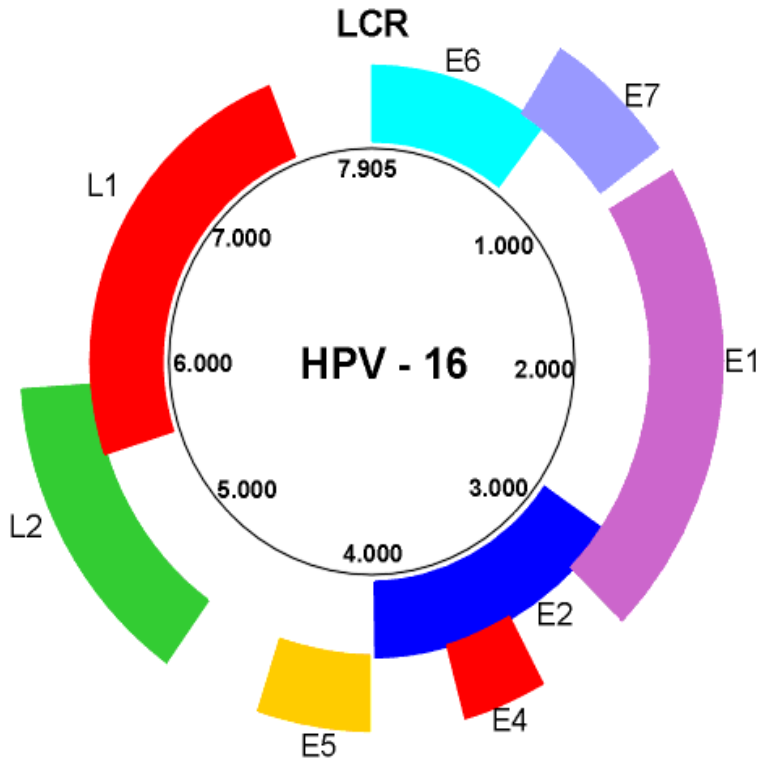
Agenda

- **HPV and cancer**
- The burden of HPV in HIV-positive patients
- Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-positive women

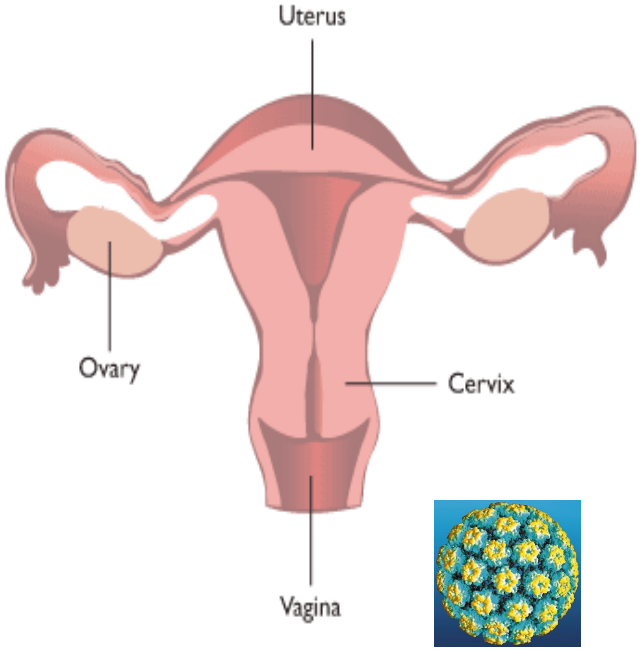
HPV: Human PapillomaVirus

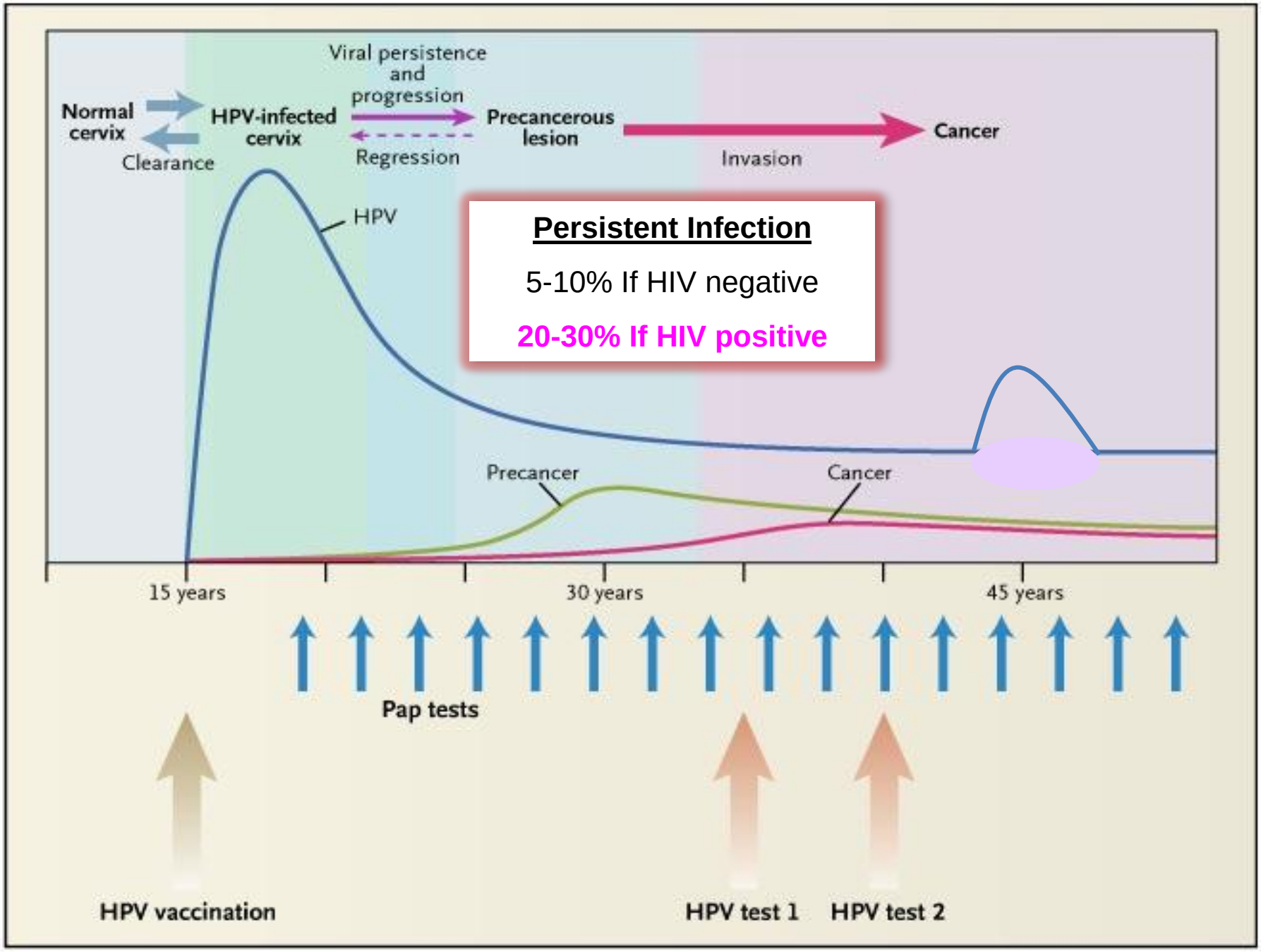




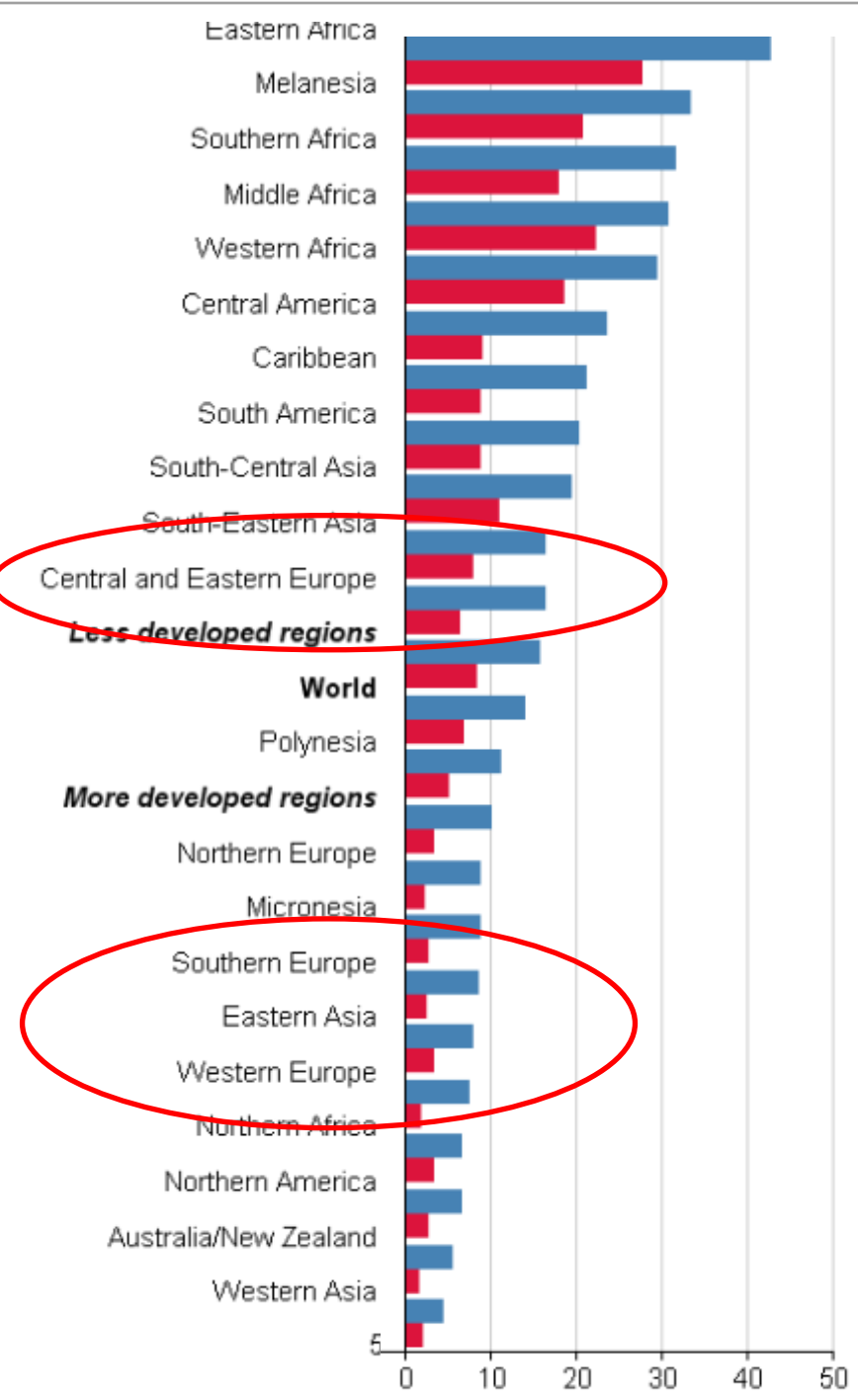


What are the HPV-induced cancers?





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



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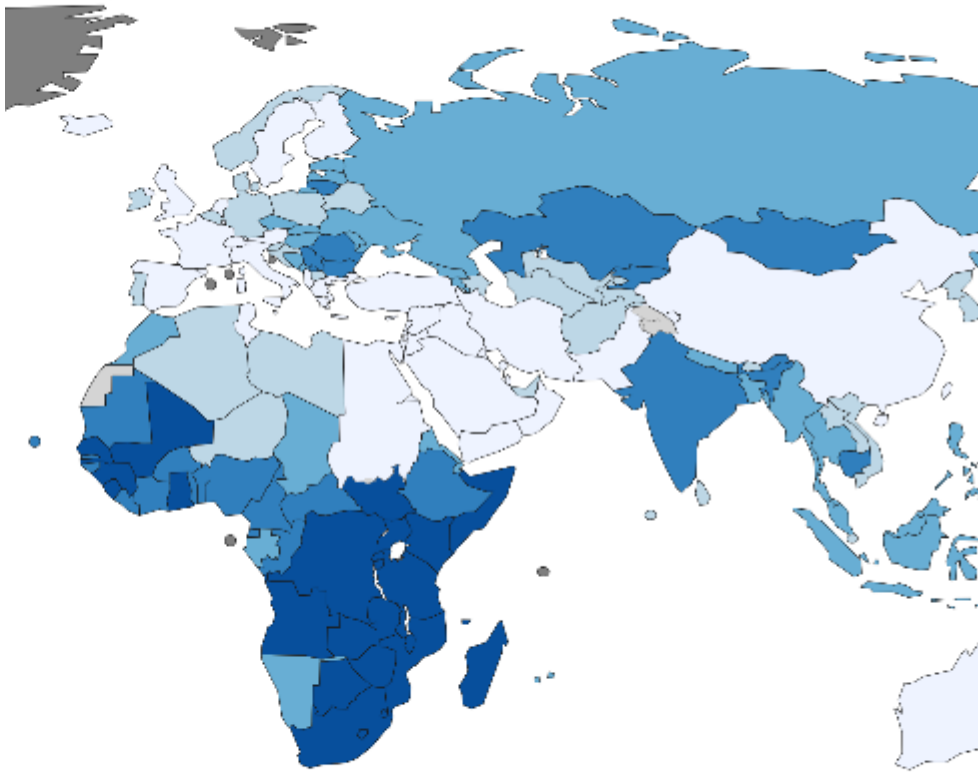

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00/ year

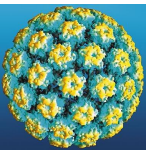
Agenda

- HPV and cancer
- **The burden of HPV in HIV-positive patients**
- Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-positive women

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

CD4 cell count decreases
HIV Viral load increases

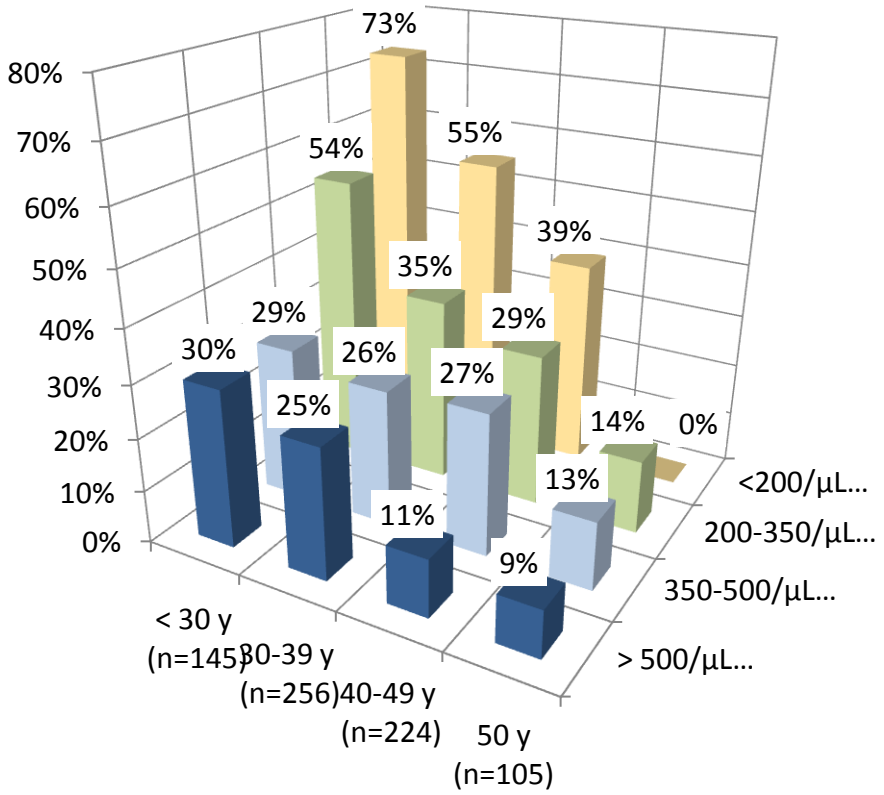
- **HPV Infection**
  - Prevalence and incidence of HPV infection are higher.
  - **HPV viral load are higher. More infections with multiple genotypes.**
  - Clearance is decreased and recurrence of latent infection are frequent.
  - Persistent infection is significantly higher.
- **Precancerous lesions**
  - Prevalence and incidence of precancerous 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 times higher for the anus



Infection by HPV and HPV-induced lesions in the cervix in HIV-positive women

- High risk HPV

	HIV+		HIV-
▪ Prevalence :	**43 %**	vs.	12% (Belgium: n=652,
▪ Prevalence	**33.2%**		(Spain: n=479,42
▪ Prevalence	**49.5%**		(MACH-1:n=518,3
▪ Incidence:	**13.4%**	vs.	5 % women-year[1]



- Cervical dysplasia

		HIV+	HIV-
• Prevalence of abnormal cytology		**38%**	vs. 16% [4]
• Prevalence in Belgium	All AC	**28%** [1]	vs. 5.9%
	HSIL	**3%**	vs. 1.2%
• Prevalence in MACH-1	AAC /HSIL	**36%/8%**	
• Prevalence in Spain	HSIL	**3.8%**	
• Incidence of abnormal cytology		**20%**	vs. 5% after 3
• Incidence in Belgium	ACC	**6% women year** [1]	
	HSIL	**1.4% women year**	

- After conisation:

Abormal cytology after conisation **66%** vs. 33% [6]

[1] Konopnicki D. PhD June 2014
[2] Stuardo V. PLOS one 2012
[3] Heard I. BJOG 2012
[4] Massad. *J Acq Imm Defic Syndr* 1999.
[5] Ellebrock. *JAMA* 2000.
[6] Gilles C. *Gynecologic Obstetric* 2005.

Epidemiology in HIV-positive patients

Study over 500,000 HIV patients linked with cancer registry data in US

	SIR
Anus (men **MSM**) AIN3/ Invasive	90/52
Anus (men **MSW**) AIN3/ Invasive	21/14
Anus (**women**) AIN3 / Invasive	33/15
Cervix CIN3/ Invasive	9/6
Oropharynx	1.6
Penis PIN3/ Invasive	20/5
Vagina or Vulva Va VIN3/ Invasive	27/6

Chaturvedi A.
J Natl Cancer Inst. 2009

Incidence per 100,000 person-years

(General Population)	1980-1989 Before ART	1990-1995 ART	1996-2004 Early HAART
Anus (men)			
AIN3	1.7	18.3	29.5
Invasive *(1)*	10.5	20.7	42.3
Anus (women)			
AIN3	0	1.7	5.2
Invasive *(1)*	0	5.2	11.2
Cervix			
CIN3	178	449	
Invasive *(50)*	71	89	90
Oropharynx *(3)*	0	3.9	6.5
Penis			
PIN3	1.7	1.7	4.2
Invasive *(1.5)*	0	1.3	2.9
Vagina or Vulva			
Va/VIN3	17	54	60
Invasive *(3)*	0	7	8

Agenda

- HPV and cancer

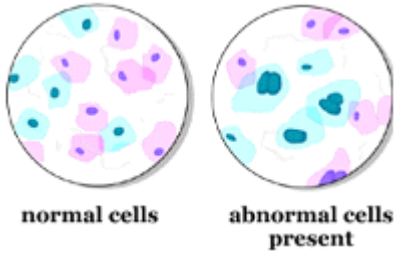
- HPV and HIV interactions
- The burden of HPV in HIV-positive patients

- **Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-positive women**

Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-positive women

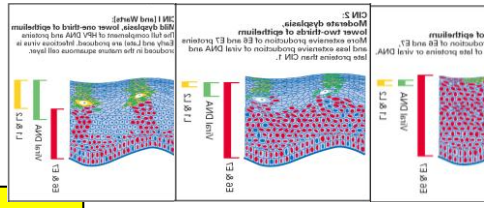
Cervical screening in developed countries

Pap-smear
+/- HPV-DNA



Normal | Ascus | LSIL | HSIL

HPV neg | HPV pos



Colposcopy + biopsy

Check after 1 year | Check after 6 months

LG CIN | HG CIN

Normal

Pap-smear after 6 months
Colposcopy + biopsy after 1 year

Conisation

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 2, 2009 VOL. 360 NO. 14

HPV Screening for Cervical Cancer in Rural India

Rengaswamy Sankaranarayanan, M.D., Bhagwan M. Nene, M.D., F.R.C.P., Surendra S. Shastri, M.D., Kasturi Jayant, M.Sc., Richard Muwonge, Ph.D., Atul M. Budukh, Ph.D., Sanjay Hingmire, B.Sc., Sylla G. Malvi, M.Sc., Ph.D., Ranjit Thorat, B.Sc., Ashok Kothari, M.D., Roshan Chinoy, M.D., Rohini Kelkar, M.D., Shubhada Kane, M.D., Sangeetha Desai, M.D., Vijay R. Keskar, M.S., Raghevendra Rajeshwarkar, M.D., Nandkumar Panse, B.Com., and Ketayun A. Dinshaw, M.D., F.R.C.R.

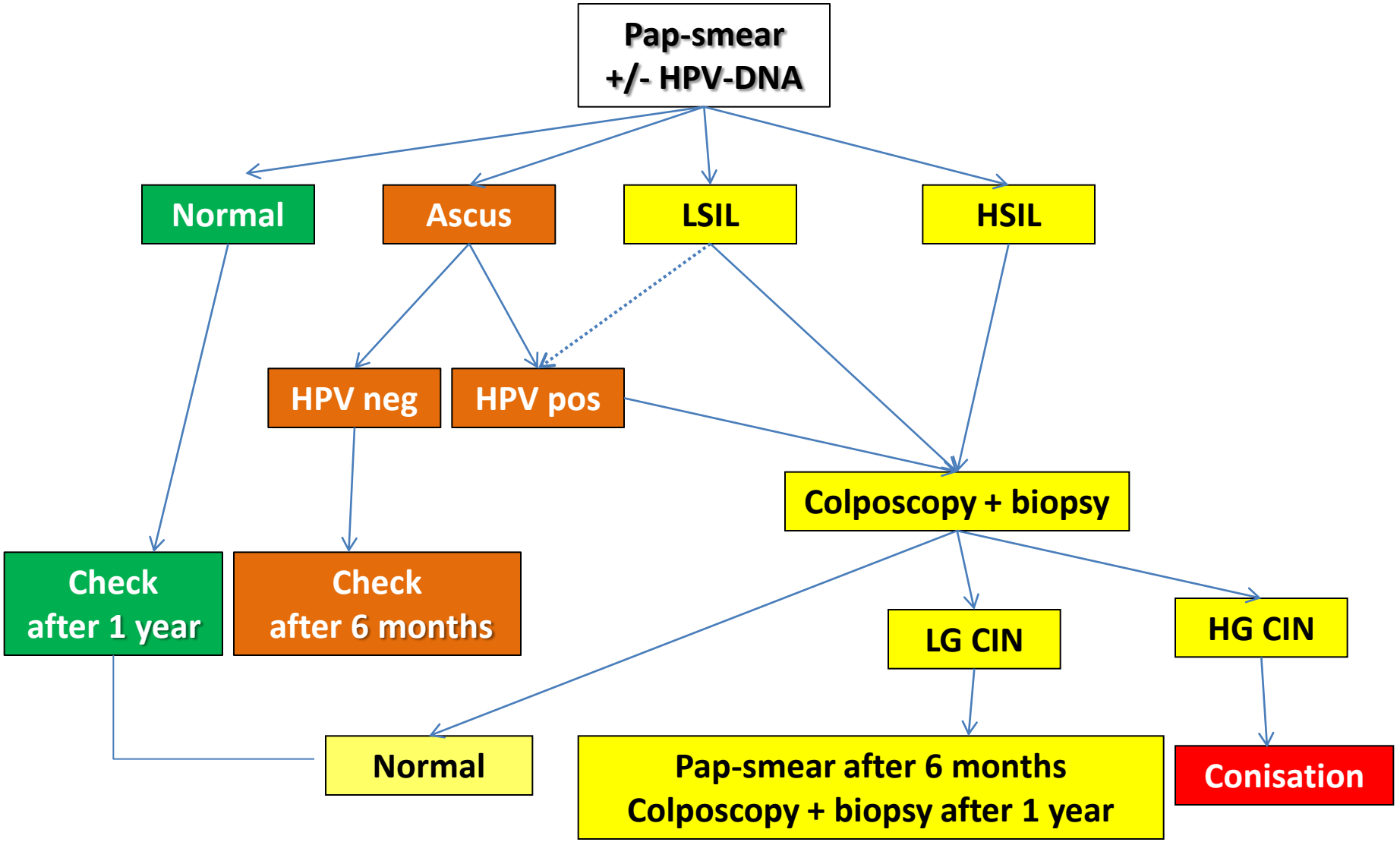
THE LANCET

Volume 385 · Number 9980 · Pages 1803-1916 · May 9-15, 2015 www.thelancet.com

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow up of four European randomised controlled trials

Ronco G. *The lancet 2014*.

Cervical screening in developed countries



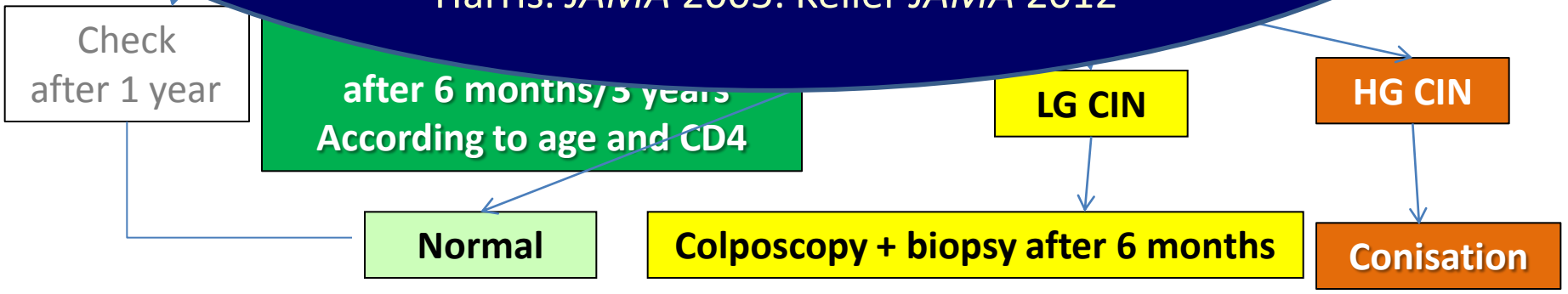
Cervical screening in developed countries

Could this be applied to HIV-positive women?

- Under 30 years HPV prevalence is too high
- After 30 years:
  - ➢ HPV testing is **cost-effective** in HIV-women
  - ➢ It has a good **Negative Predictive Value** for women with CD4>500/µL.

These women could be screened at longer interval.

Harris. *JAMA* 2005. Keller *JAMA* 2012



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

Screening for cervical cancer in developped countries

- Refer for screening at the first consultation
- If ≥30 years
  - Test for HRHPV
    - If HPV positive: colposcopy/biopsy
    - If HPV negative : next screen can be after
      - 3-5 years if CD4 high (>500/µL) and under cART
      - 1 year in other cases
- If <30 years
  - Cytology and colposcopy/biopsy

Should we screen women for anal cancer?

- In the general population, anal cancer is more frequent in women then men but remains rare
  - 1/100,000 in men
  - 2/100,000 in women

- **In HIV-positive women**

Silverberg M and al. CID 2012

	HIV-Infected			HIV-Uninfected	
	MSM	Other Men	Women	Men	Women
Baseline characteristics					
No.	18 855[a]	6492[a]	8842	102 607	11 653
Cases	122	14	15	13	0
Person-years	93 063	30 570	49 676	585 049	67 942
Median years follow-up (IQR)	4.0 (1.6–7.8)	3.9 (1.6–7.2)	5.3 (2.0–8.8)	4.7 (2.0–10.0)	5.0 (2.1–9.9)
Incidence rate per 100 000 person-years (95% CI)	131 (109–157)	46 (25–77)	30 (17–50)	2 (1–4)	0 (0–5)
Rate ratio (95% CI)	80.3 (42.7–151.1)[d]	26.7 (11.5–61.7)[d]	Undefined[e]	Reference	Undefined[e]

There are limitations

SYSTEMATIC REVIEW, META-ANALYSIS, NARRATIVE REVIEW

Journal of Lower genital Tract Disease. July 2015

Screening for Anal Cancer in Women

Anna-Barbara Moscicki, MD,[1] Teresa M. Darragh, MD,[2] J. Michael Berry-Lawhorn, MD,[3] Jennifer M. Roberts, MBBS, FRCPA,[4] Michelle J. Khan, MD, MPH,[5] Lori A. Boardman, MD, ScM,[6] Elizabeth Chiao, MD, MPH,[7] Mark H. Einstein, MD, MS, FACOG, FACS,[8] Stephen E. Goldstone, MD,[9] Naomi Jay, PhD,[10] Wendy M. Likes, PhD, DNSc, APRN-Bc,[11] Elizabeth A. Stier, MD,[12] Mark L. Welton, MD, MHCM,[13] Dorothy J. Wiley, PhD,[14] and Joel M. Palefsky, MD[15]

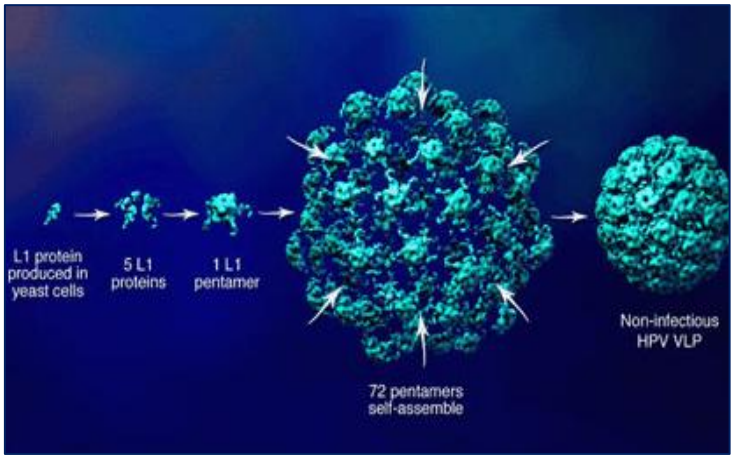
- Technical:
  - Digital anorectal examination (DARE): no guidelines
  - Anal cytology: poor correlation with the level of dysplasia
  - igh resolution anoscopy: is golden standard but costly, timely and few teams are proprely trained
- Scientific:
  - No randomised study showed a decrease in mortality after anal cancer screening implementation either by DARE/cytology/HRA
  - One randomised study is ongoing NCT01946139 to evaluate the best technique HPV testing/cytology/HRA in women
  - The ANCHOR study (NTC02135419) is designed to determine whether treating AIN2/3 in HIV-infected persons >35 y will prevent anal cancer

Proposal

- **All HIV-positive women: DARE and routine assessment of anal symptoms**
- **Cytology and HRA in women at higher risk of cancer**
  - **If CD4 nadir low: < 50-200 lymphocytes CD4/µl**
  - **If other HPV-related cancer**

Preventive Vaccines

External capsid:
L1 protein



Bivalent (BHPV)

Cervarix®GSK:

HPV 16/18 + ASO4
(monophosphoryl lipid A = detoxified derivative of LPS of Salmonella adsorbed on aluminium)

Approval by EMA & FDA:

2007

- Females
- Precancerous lesions in the cervix, vulva or vagina
- Cervical cancer

Quadrivalent (QHPV)

Gardasil®Merck:

HPV 6/11 + 16/18

2006

- Females and males
- Precancerous lesions in the cervix, vulva or vagina and anus
- Cervical and anal cancers
- Genital warts

Ninevalent (NHPV)

Gardasil9®Merck:

HPV 6/11 + 16/18/31/33/45/52/58

2014/15

- Females and males
- Precancerous lesions in the cervix, vulva or vagina and anus
- Genital warts

Preventive Vaccine in HIV-negative population

- Very efficient against HRHPV vaccinal types of

	Infection	Dysplasia
• Young women: cervix, vulva/vagina	yes	yes
• Women 26-45 years	yes	yes
• Young women : anus, oral	yes	
• Young men : condyloma/ perianal	yes	yes
• Young MSM: HGAIN	yes	yes

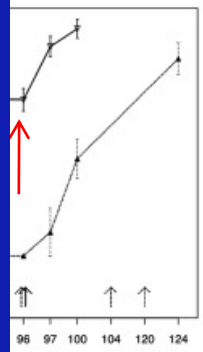
- Safe
- Long term protection: immunogenicity up to 10 years
- Recommended by
  - ➢ WHO: girls
  - ➢ ECDC (2008-2012) : girls
  - ➢ US, Canada, Australia: girls and boys and MSM up to 26 y

Preventive vaccine in HIV+patients

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

Immunobridging studies

What about clinical efficacy ?



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and 4

Concerns in HIV patients

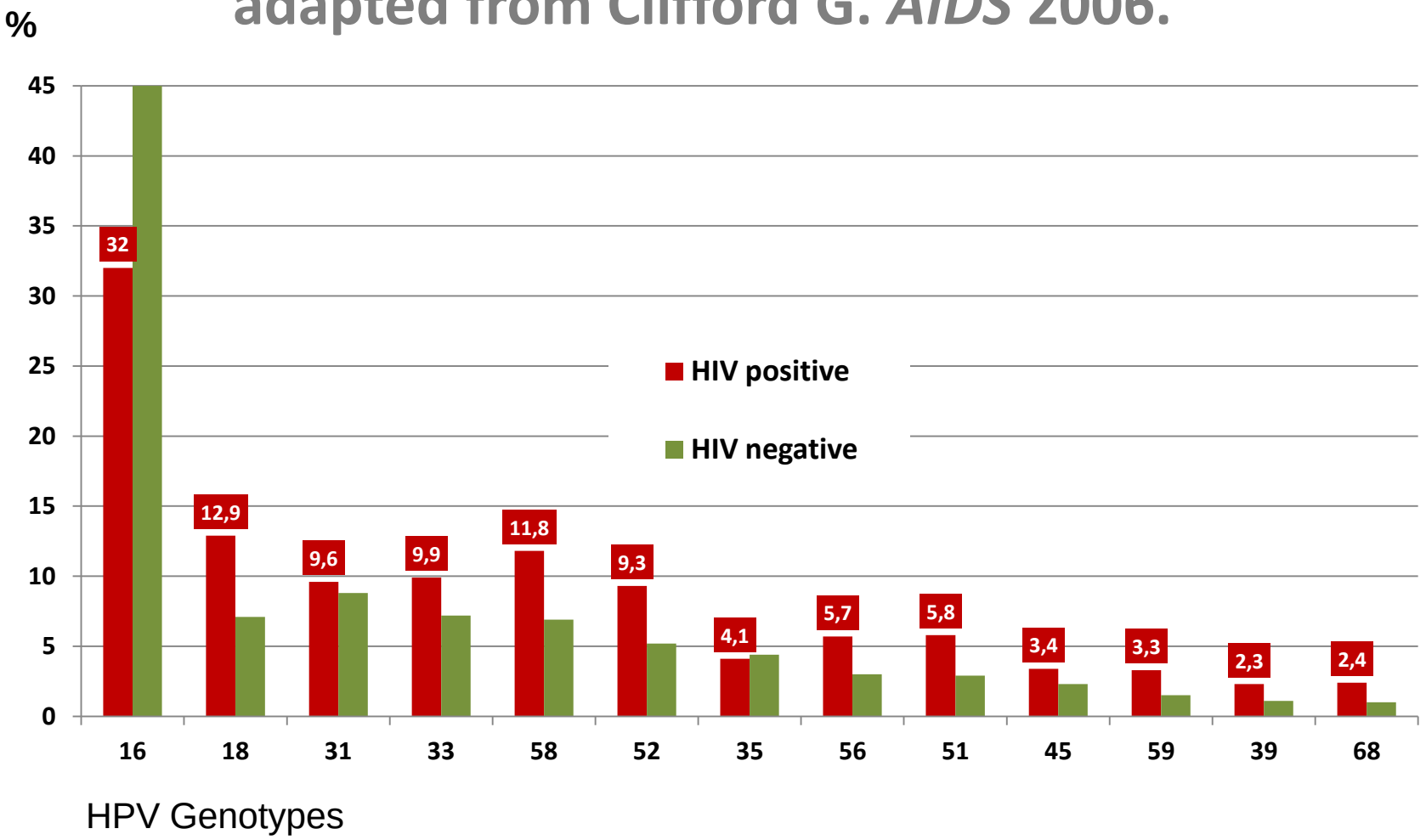
- **Cost?**
  - in most european countries , HPV vaccination is recommended for girls 9-13 with catch up program and thus reimbursed 65-100% by the national health authorities
  - 200- 375 € for 3 doses
- **How many doses?**
  - Can we give 2 doses before 15 years?
  - Could even one dose be enough?

No data in HIV-positive patients!

- **Do we cover all HRHPV genotypes?**

HPV genotype distribution in HG CIN in HIV positive and negative women

adapted from Clifford G. *AIDS* 2006.



Proportion of women infected with HRHPV genotypes that are included in the different vaccines

Prevalence of women of whom all or a part of HRHPV types are covered by	Current HPV vaccines including HRHPV 16 /18	Ninevalent HPV vaccine including HRHPV 16/18/31/33/45/52/58
Among all women (n=116)	24%	79%
Among women with abnormal cytology (n=44)	27%	82%

Konopnicki D and al.
Accepted in AIDS 2015

Is vaccination indicated in patients with high grade lesions as secondary prophylaxis?

Women (HIV-negative)

- 2 randomised studies: Joura E. *BMJ* 2012.Woo Dae Kang. *Gynecol Oncol* 2013
- Decreased in recurrent lesions
  - **-65%** 2 years after treatment of CIN2-3 and vaccination
  - **-35%** 2 years after treatment of condyloma and vaccination

2.5% had recurrent CIN 2-3 among women vaccinated

vs 7.2% in non vaccinated women

How does it work?

- Strong HPV specific cell mediated immune responses in HIV-infected adolescents and young adults similar to HIV-negative
- 46 young adolescents/adults followed up to 28 weeks

Rainone V and al. AIDS 2015

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**
  - Women up to 45 years

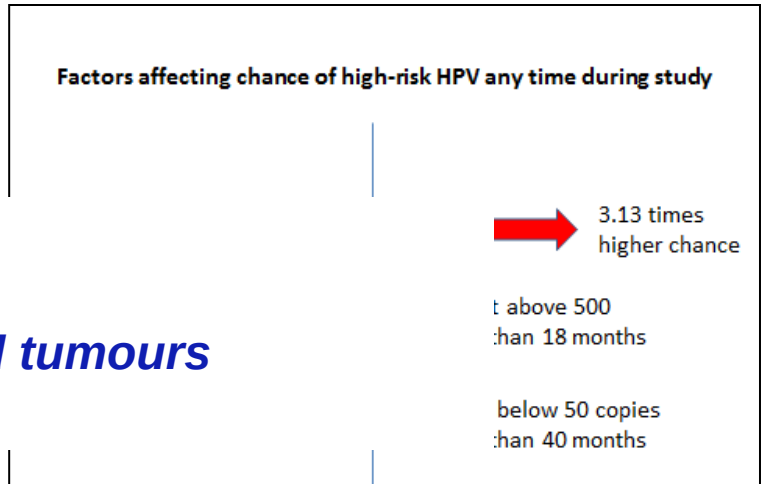
Does cART prevent HPV infections or HPV- induced lesions?

…more recently

FEMAL

Cohort of 652 women, 38 years,
successfully treated for HIV
FU 61 months
Sustained viral su
reduces the risk o
Konopnicki D. *JID*

PS5/4
Thursday 22 Oct 15 PM
Opportunistic infection and tumours
Room Cologne



…this might mean

…that patients with HG lesions or at risk (HRHPV+) should be treated by cART whatever the CD4 cell count is…

…prospective randomised studies on this issue would not be ethical as the CD4 lymphocyte count threshold for treating HIV-patients has raised…

So the answer might come from cohort studies after several years

Conclusion: in HIV-infected women

- Infection with HPV and HPV-related cancerous lesions are more frequent and severe .
- **Preventive vaccines against HPV are safe and immunogenic: they should be implemented in HIV-infected children and adults.**
- HPV testing for primary cervical screening could become the gold standard in women after 30 years.
- Studies on anal cancer screening and treatment in women are ongoing
- **cART decreases infection by HRHPV and induced lesions but favourable impact appears after several years.**