Prevention and management of HPV related tumors in HIV positive individuals

Mario Poljak

Institute of Microbiology and Immunology
Faculty of Medicine, University of Ljubljana, Slovenia
Slide withheld at request of author
The Nobel Prize in Physiology or Medicine 2008

"for his discovery of human papilloma viruses causing cervical cancer"

Harald zur Hausen

1/2 of the prize

Germany

German Cancer Research Centre
Heidelberg, Germany

b. 1936

"for their discovery of human immunodeficiency virus"

Françoise Barré-Sinoussi

1/4 of the prize

France

Regulation of Retroviral Infections Unit, Virology Department, Institut Pasteur
Paris, France

b. 1947

Luc Montagnier

1/4 of the prize

France

World Foundation for AIDS Research and Prevention
Paris, France

b. 1932
Much progress has been made in the development of tools to prevent, diagnose and treat HIV infection. However, we still do not have a vaccine and antiretroviral treatments are not curative as HIV persists in many compartments of the body. The implementation of these tools at large scale worldwide remains a critical challenge as well as the sustainability of these life-long therapies. Recent advances in our understanding of protective immune responses and of HIV persistence have generated some optimism about the development of novel vaccine and HIV cure strategies, which are an absolute necessity to end the HIV epidemics.
Conclusions (i)

HIV+  ▶▶  HPV  incidence persistence prevalence

HPV+  ▶▶  HIV  incidence prevalence
Conclusions (ii)
Slide withheld at request of author
HPV
Viral characteristics

- non-enveloped viruses; icosahedral capsid

- remarkably diverse BUT remarkably genetically stable (diverged since the origin of humanity only by about 2%)

- classified by the homology of their genome into many genotypes

- genotypes numbered chronologically in order of characterization

- 207 official HPV genotypes (as of April 24, 2017)
Slide withheld at request of author
High-risk alpha HPV genotypes - related cancers

HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59
Low-risk alpha HPV genotypes
HPV-6, HPV-11
Higher HPV prevalence in comparison to HIV negatives (60-75% vs. 25-30%).

More likely to have infection with multiple HPV types.

Increased risk of persistent infection with oncogenic HPV and higher likelihood of development of malignancy; HPV persistence nearly doubles if CD4 < 200 cells/mm3.

3 x more likely to have LSIL; 5 x more likely to have HSIL.

SILs progress more rapidly, more resistant to therapy and more frequently recur.

Higher rate of underlying histologic CIN3+; SILs treatment failures significantly higher.

5-22 x higher risk of cervical cancer.

More parametrial invasion and higher FIGO stage at presentation.

More residual disease at first follow-up (51% vs. 28%).

Shorter time to progression (0.64 years vs. 1.8 years) and death.

Clifford GM et al. AIDS 2006; 20: 2337-2334.
Human Papillomavirus Prevalence and Type Distribution in 3603 HIV-Positive and HIV-Negative Women in the General Population of Tanzania: The PROTECT Study

Myassa Dartell, MD, MSc,**† Vibeke Rasch, MD, DMsc,**‡ Crispin Kahesa, MD,§ Julius Mwaiselage, MD,§ Twalib Ngoma, MD,§ Jette Junge, MD,¶ Anne Gernow, MD,¶ Sussie Funch Ejlerson, CT,¶ Christian Munk, MD, PhD,† Thomas Ifiner, PhD,¶ and Susanne Krüger Kjaer, MD, DMsc†**
Cumulative probability of newly detected HPV infection by study cohort; incident HIV cohort (n=94); prevalent HIV group (n=297); HIV-negative group (n=3,799)
Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis

Dorothy A Machalek, Mary Poynten, Fengyi Jin, Christopher K Fairley, Annabelle Farnsworth, Suzanne M Garland, Richard J Hillman, Kathy Petoumenos, Jennifer Roberts, Sephr N Tabrizi, David J Templeton, Andrew E Grulich

Prevalence of any high-risk HPV type (% [95% CI])

HIV-positive
  - 88.7 (85.5–91.9)
  - 68.7 (57.6–79.8)
  - 85.0 (69.4–100)
  - 71.9 (56.3–87.5)
  - 79.5 (74.2–84.8)
  - 94.4 (87.0–100)
- Chin-Hong et al (2008) 34: 38
  - 71.1 (55.6–85.5)
  - 48.9 (34.3–63.5)
- Lacey et al (1999) 40: 54
  - 85.2 (75.7–94.7)
  - 55.9 (50.5–61.3)
  - 56.6 (47.9–64.7)
- Overall: 1352
  - 73.5 (63.9–83.0)

HIV-negative
- Nyitray et al (2011) 35: 176
  - 27.3 (20.7–33.9)
  - 51.7 (42.6–60.8)
  - 30.9 (20.8–40.9)
  - 73.1 (64.1–82.1)
  - 34.5 (24.5–44.5)
  - 25.6 (23.2–28.1)
  - 28.9 (23.7–34.2)
- Friedman et al (1998) 43: 45
  - 26.7 (12.8–39.6)
- Overall: 2103
  - 37.2 (27.4–47.0)

\( I^2 = 94.2\% \); \( p < 0.0001 \)

\( I^2 = 94.4\% \); \( p < 0.0001 \)
Oral human papillomavirus infection in HIV-negative and HIV-infected MSM

Sofie H. Mooij\textsuperscript{a,e}, Hein J. Boot\textsuperscript{b,†}, Arjen G.C.L. Speksnijder\textsuperscript{a},

AIDS 2013; 27: 2117–2128
HIV+ incidence persistence prevalence

HPV incidence prevalence

HPV+ incidence prevalence

HIV prevalence
HPV+ → HIV

risk of HIV acquisition significantly associated with HPV infection in largest meta-analysis, N=6,567 patients; summary OR=1.96 (95% CI 1.55 to 2.49)

risk doubles with any high-risk HPV genotype; OR=2.06 (95% CI: 1.44–2.94)

HPV could predispose to HIV infection and dissemination through its disruption of the epithelium integrity and the mucosal immune system by several mechanisms

Lissouba P al. Sex Transm Infect 2013; 89: 350-356
PREVENTION

ABC
cART
HPV vaccination
anal PAP screening
cervical screening (PAP, HPV)
circumcision
Slide withheld at request of author
PREVENTION

- ABC
- cART
- HPV vaccination
- anal PAP screening

- cervical screening (PAP, HPV)
- circumcision

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cART and HPV prevalence and persistence

- lower HPV prevalence and less HPV types in cART patients (up to 77%)
- cART associated with a decreased risk of persistent HPV infection


- prolonged cART use may be associated with reduction of the incidence and progression of cervical and anal dysplasia

prospective cohort of 1,238 women living with HIV/AIDS in Burkina Faso and South Africa; recruitment stratified by cART status

CIN2+ incidence reduced among women on cART (OR = 0.39, 95% CI 0.15-1.01).

prolonged and effective cART is important in controlling hr-HPV and CIN2+ development
320 HIV-positive MSM

median CD4+ T lymphocytes of 638 cells/mL

87% on cART for a median of 5 years

significantly fewer anal HSIL in patients with cART ≥24 months = OR 0.32 (CI 95% 0.162-0.631)

prolonged cART (≥24 months) is associated with fewer anal HSIL
cART and HPV prevalence and persistence

- lower HPV prevalence and less HPV types in cART patients (up to 77%)
- cART associated with a decreased risk of persistent HPV infection


- prolonged cART use may be associated with reduction of the incidence and progression of cervical and anal dysplasia


BUT

- the incidence of HPV-related cancers has not declined (cervical cancer) or it has even increased (anal cancer) since the introduction of cART
Incidence of anal cancer in men who have sex with men, by HIV status

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HAART era (from 1996)

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Pre-HAART era (before 1996)

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HIV-negative

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cART and HPV prevalence and persistence

- lower HPV prevalence and less HPV types in cART patients (up to 77%)
- cART associated with a decreased risk of persistent HPV infection


- prolonged cART use may be associated with reduction of the incidence and progression of cervical and anal dysplasia


BUT

- the incidence of HPV-related cancers has not declined (cervical cancer) or it has even increased (anal cancer) since the introduction of cART
- prolonged survival provides more time to potentially develop the cervical and anal cancer and other non-HPV related cancers
Cancer risk among the HIV-infected elderly in the United States

Elizabeth L. Yanik, Hormuzd A. Katki and Eric A. Engels

Objective: HIV-infected people and elderly people have higher cancer risk, but the combined effects of aging and HIV are not well described. We aimed to evaluate the magnitude of cancer risk in the HIV-infected elderly population.

Design: We conducted a case-cohort study including a 5% sample of U.S. Medicare enrollees and all cancer cases aged at least 65 in linked cancer registries.

Methods: HIV was identified through Medicare claims. Among the HIV-infected, absolute cancer risk was calculated accounting for the competing risk of death. Associations between HIV and cancer were estimated with weighted Cox regression adjusting for demographic characteristics.

Results: Among 469,954 people in the 5% sample, 0.08% had an HIV diagnosis. Overall, 825,776 cancer cases were identified in cancer registries. Over 5 years, 10.1% of the HIV-infected elderly developed cancer, the most common diagnoses comprising lung (5-year cumulative incidence = 2.2%), prostate (2.7%, among men), and colorectal cancer (0.9%), and non-Hodgkin lymphoma (0.8%). HIV was strongly associated with incidence of Kaposi sarcoma [adjusted hazard ratio (aHR)=94.4, 95% confidence interval (95%CI)=54.6–163], anal cancer (aHR=34.2, 95%CI=23.9–49.0) and Hodgkin lymphoma (aHR=6.3, 95%CI=2.8–14.3). HIV was also associated with incidence of liver cancer, non-Hodgkin lymphoma and lung cancer (aHR=3.4, 2.6, and 1.6, respectively).

Conclusion: In the elderly, HIV infection is associated with higher risk for many cancers, although some associations were weaker than expected, perhaps reflecting effects of non-HIV pathways on cancer development. Due to the effects of HIV and aging, the HIV-infected elderly have a sizeable absolute risk, highlighting a need for cancer prevention.

AIDS 2016, 30:1663–1668
PREVENTION

ABC

cART

HPV vaccination

anal PAP screening

cervical screening (PAP, HPV)
circumcision
Prophylactic HPV vaccines

2vHPV: 16 and 18 with ASO4

4vHPV: 6, 11, 16 and 18

9vHPV: 6, 11, 16, 18, 31, 33, 45, 52 and 58

L1 viral like particles
Two doses are recommended for persons starting the series before their 15th birthday.

Three doses are recommended for those who start the series on or after their 15th birthday and for persons with certain immunocompromising conditions.
- IgG antibodies (transudation and exudation)
- heterogeneous mixture of neutralizing and non-neutralizing antibodies
- an immunologic correlate with protection not established yet !!!
Natural HPV infection

women:
- 54%-69% seroconvert
- low-level antibodies
- partial protection against reinfection

men:
- 7%-10% seroconvert
- low-level antibodies
- no protection against reinfection

**BUT:** nearly 100% seroconversion following HPV vaccination in both genders!

HPV vaccination is the only reliable method to ensure immune protection against new HPV infections and subsequent disease in males.
Why are HPV vaccines “better” than nature?

Natural HPV infection:
- no viraemia, poor access of virus to lymph nodes

HPV vaccination:
- vaccine delivered intramuscularly
- rapid access of VLPs to blood vessels and local lymph nodes

BONUS

VLPs are very immunogenic:
- display many neutralising epitopes (more than native virion)
- induce good T-cell helper responses for B-cells
  - important for robust antibody and B-cell memory responses
98-100% efficacy against anogenital lesions caused by targeted HPV types in several large international randomized, double-blind trials.
HPV infections (vaccine types)

genital warts

CIN 2/3

time

? cancer
All three HPV vaccines have excellent safety and efficacy profiles.
Countries with current or planned use of HPV vaccine in the national immunization programme (January 2017)

- GAVI supported nationwide introduction = 2 countries
- GAVI demo projects (started to date) = 14 countries
- GAVI demo projects (start 2015/2016) = 7 countries

Abbreviation: Gavi = Gavi, the Vaccine Alliance.
Number of people vaccinated through HPV national vaccination programmes globally (by the end of 2016)

- 78 million girls/women have received at least one-dose of HPV vaccine through national HPV vaccination programmes
- 61 million girls/women received full course vaccination
- 12 million boys/men have received at least one-dose of HPV vaccine through national HPV vaccination programmes
- 6 million boys/men received full course vaccination

Bruni L. et al. IPV Meeting 2017, Capetown, unpublished data
Human papillomavirus vaccines in 2017

Safe
Effective
Underused

(especially in males)

(exceptionally used in HIV+ individuals)
Slide withheld at request of author
HPV vaccination of HIV+ individuals

- The efficacy trials of HPV vaccines excluded HIV+ individuals.
- 9 studies of safety and immunogenicity in HIV+ children or adults.
- Single study of persistence of immunogenicity up to 5 years in HIV+ children.
- No efficacy studies (with hard endpoints) in HIV+ adolescents and young adults.

An efficacy study of 4vHPV in HIV+ adults (average age 47 years of age) was stopped early based on the results of the futility analysis.
Safety and immunogenicity and persistence of immune responses to HPV vaccine in HIV+ children

- HPV vaccine was generally safe and well tolerated; no safety signals
- 99.5% seroconversion to all HPV genotypes in the vaccinees
- Antibody concentrations comparable to historical HIV-negative age-matched controls
- High plasma HIV RNA correlated with decreased antibody responses
- Sporadic correlations of CD4+ with antibody responses
Safety and immunogenicity of HPV vaccine in HIV+ adolescents and adults

- studies included participants 13 to 45 years of age followed for ≤24 months

- no safety issues

- generally robust antibody responses that positively correlated with high antibody concentrations at baseline, low plasma HIV RNA copies/mL, cART administration, and high CD4+T cells

- comparisons with HIV-negative age-matched historical controls showed variable results, but consistently lower antibody concentrations in HIV+ without cART vs. HIV-negative vaccinees
current HPV vaccines are highly immunogenic and have acceptable safety and tolerability profiles in HIV+ hosts; however whether there will be any difference in HPV vaccine efficacy between HIV+ and HIV-negative persons is unclear at present.

HIV+ hosts >26 years of age, those with uncontrolled HIV replication and those with low CD4+ T cells have lower antibody response to HPV vaccines than HIV-negative age-matched historical controls.

Immunogenicity of 2 doses of HPV vaccines may not be similar to that of 3 doses in HIV+.

Additional doses (4th, 5th) of HPV vaccines increase the antibody and T-cell memory response to vaccine genotypes.

HIV+ vaccinee with uncontrolled HIV replication may not be protected by HPV vaccine.

distribution of HPV genotypes may differ between HIV+ and HIV-negative individuals in the same community.

Herd immunity conferred by HPV mass immunization may be lower in areas with high prevalence of HIV infection.
HPV vaccination is recommended through age 26 years for men who have sex with men and for immunocompromised persons (including those with HIV infection of both genders) who have not been vaccinated previously or have not completed the 3-dose series.

CDC
WHO
IDSA
EACS
IAS-USA
American Cancer Society
US Department of Health and Human Services (AIDS info)
PREVENTION

ABC
cART
HPV vaccination
anal PAP screening

cervical screening (PAP, HPV)
circumcision
secondary prevention (screening) + primary prevention (vaccination)
primary and secondary prevention act additively by intervening at different points in the natural history of cervical cancer and imply actions in women of different ages
Cervical cancer prevention strategies

- 1945 +
  - Cytology x 3 yrs.

- 2006 +
  - Cytology (x3 to age 25/30) & HPV test x 5/10 yrs.
Screening for cervical cancer in women living with HIV

Women diagnosed with HIV should as soon as possible be referred for a cervical cancer screening.

Women aged 23-29 living with HIV should be screened upon initiation of care, test should be repeated at 6 months and annually thereafter if results are normal.

Women aged 30-64 living with HIV should be offered cervical cancer screening with cytology and HPV test; when the patient is free from HPV and her cytology is normal, she can be followed once every third year.

Women living with HIV with normal cervical cytology and negative HPV result have the same 5-year risk of developing cervical pre-cancer as HIV-negative women, irrespective of CD4 counts.

Keller MJ et al. JAMA 2012; 308: 362-369
retrospective cohort study

238 women with a history of HIV, previous hysterectomy and no previous abnormal Pap test results; median follow-up time 16 years

more than 30% of HIV-infected women had abnormal vaginal Pap test results

23 x VAIN-1, 9 x VAIN-2 and 7 x VAIN-3

HIV+ women should continue with regular vaginal Pap testing after hysterectomy!
PREVENTION

ABC

cART

HPV vaccination

anal PAP screening

cervical screening (PAP, HPV)
circumcision
Incidence of anal cancer in men who have sex with men, by HIV status

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Screening for anal cancer in PLHIV and MSMs

anal cancer almost exclusively caused by HPV, mainly HPV-16

prevalence of AIN3 and anal cancer is 5-50 times higher among HIV positive MSM and comparable to the prevalence of cervical cancer in women before cervical cancer screening was introduced

rates of AIN3 have risen more rapidly among men than among women; increase could be attributable to true increases or more aggressive screening among MSM in certain areas, facilitating diagnosis

HPV testing cannot be used as screening tool since prevalence of HPV infection is very high among both PLHIV and MSM
Proposed algorithm for screening for anal cancer and precursors in HIV-infected patients


*This category comprises the former histopathologic nomenclature of anal intraepithelial neoplasia 2 and 3, as well as carcinoma in situ.
Anal-Rectal Cytology: The Other Pap Test

Sarah M. Bean, MD,1 David C. Chhieng, MD, MBA, MSHI2
(1Department of Pathology, Duke University Medical Center, Durham, NC, 2Department of Pathology, Yale University, New Haven, CT)

Abstract
Anal cancer screening programs are gaining momentum within the United States and Europe. The goal of such programs is to detect and eradicate human papillomavirus (HPV) related intraepithelial lesions of the anal canal before progression to invasive squamous cell carcinoma occurs. Programs are designed to screen the anal-rectal transformation zone of a highly selected group of at-risk patients using exfoliative cytology techniques, comparable to the cervical Pap test. Patients with abnormal cytology results should be referred for anoscopy, during which the anal-rectal mucosa will be carefully visually inspected by a qualified physician. Abnormal areas are biopsied for definitive histological diagnosis, and treatment should be offered as appropriate. A comprehensive anal cancer screening program should offer screening, anoscopy when indicated, and treatment for affected patients as clinically appropriate.

After reading this article, readers should be able to describe the changing epidemiology of anal squamous cell carcinoma, describe the components of an anal screening program, understand how anal-rectal cytology specimens are collected, prepared, and evaluated, and understand how abnormal anal-rectal cytology tests are followed-up.

Cytology exam 31002 questions and corresponding answer form are located after this CE Update on page 172.
Slide withheld at request of author
Screening for anal cancer in PLHIV and MSMs

**IDSA (2014)**
...all HIV infected persons with genital warts should have annual anal Pap test (weak recommendation, moderate quality evidence)....

**European AIDS Clinical Society (EACS) (2016)**
...digital rectal exam ± anal cytology every 1-3 years...

**WHO (2016)**
...screening can be performed for anal cancer and its precursors....

there is currently no strong scientific evidence and/or no practical possibility of introducing cytology-based screening for anal cancer in majority of hospitals/offices

sensitivity and specificity of anal cytology may vary substantially

high-resolution anoscopy is more complex then colposcopy because visualization of the entire squamocolumnar junction requires substantial manipulation, and its accuracy has not been systematically evaluated
Slide withheld at request of author
PREVENTION

ABC
cART
HPV vaccination
anal PAP screening

cervical screening (PAP, HPV)
circumcision
Association between male circumcision and prevalence of any penile HPV genotypes among predominantly HIV negative populations.
Association between male circumcision and prevalence of any penile anogenital warts among predominantly HIV negative populations.
PREVENTION

- ABC
- cART
- HPV vaccination
- anal PAP screening
- cervical screening (PAP, HPV)
- circumcision

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