

HPV - all it can do... Now, what we can do??

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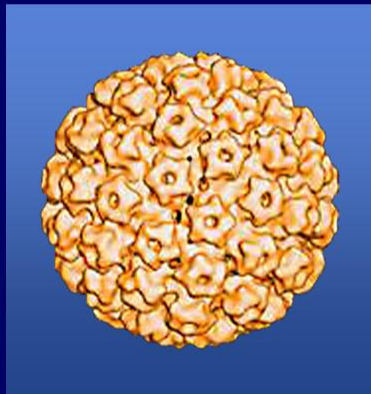


Epidemiology of HPV

- 6.2 million infected annually
- 100 serotypes
- 40 + that affect/ infect anogenital area
- Divided into high risk and low risk serotypes
- Most infections are asymptomatic or sub-clinical and **regress/ clear over time**

HPV

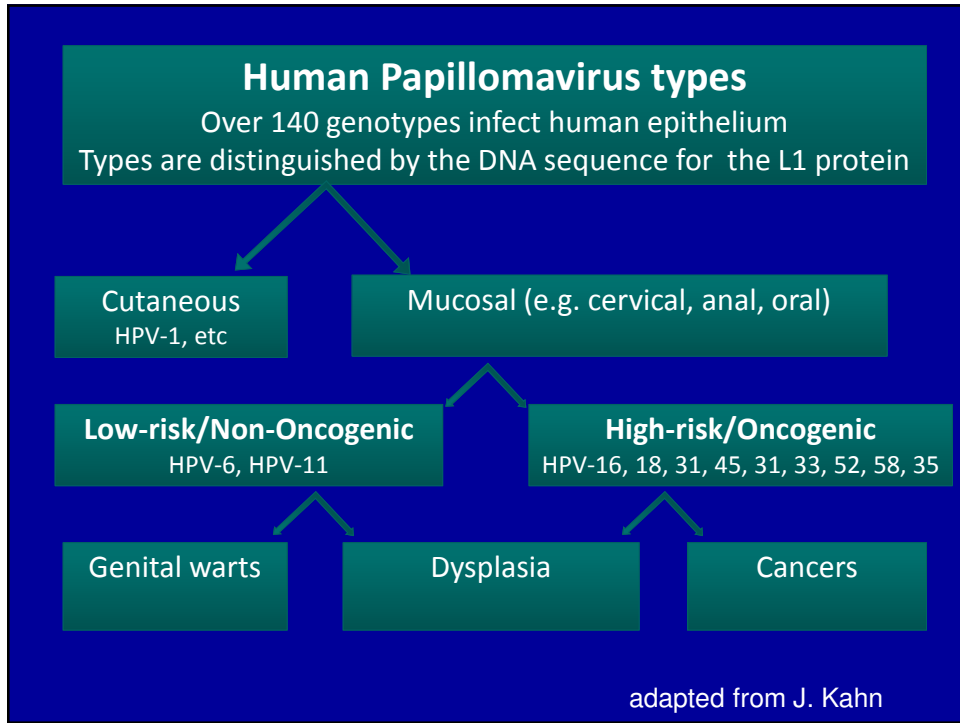
Nonenveloped double-stranded DNA virus¹



- >100 types identified²
- 30–40 anogenital^{2,3}
 - 15–20 oncogenic*^{2,3} types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 58⁴
 - HPV 16 (54%) and HPV 18 (13%) account for the majority of worldwide cervical cancers.⁵
 - Nononcogenic† types include: 6, 11, 40, 42, 43, 44, 54⁴
 - HPV 6 and 11 are most often associated with external genital warts.³

*High risk, †Low risk

1. Howley PM. In: Fields BN, Knipe DM, Howley PM, eds. Philadelphia, Pa: Lippincott-Raven; 1996:2045–2076.
 2. Schiffman M, Castle PE. *Arch Pathol Lab Med.* 2003;127:930–934. 3. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis.* 2002;35(suppl 2):S210–S224. 4. Muñoz N, Bosch FX, de Sanjosé S, et al. *N Engl J Med.* 2003;348:518–527.
 5. Clifford GM, Smith JS, Aguado T, Franceschi S. *Br J Cancer.* 2003;89:101–105.



HPV and Cancer¹

Cancer	% Associated With Certain HPV Types
Cervical*	≥95%
Vaginal*	50%
Vulvar*	>50%
Penile	50%
Anal	>70%
Oropharyngeal	20%
Nonmelanoma skin/cutaneous squamous cell	90%†

*Includes cancer and intraepithelial neoplasia
 †Immunocompromised patients
 1. Gonzalez Inxaurreaga MA, Stankovic R, Sorli R, Trevisan G. *Acta Dermatovenerol.* 2002;11:1-8.

Common HPV types

- High Risk
 - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59



- Low Risk
 - 6, 11



Estimated Annual Incidence of HPV Cervical Infection/Dysplasia¹

Cervical Infection/Dysplasia	United States	Worldwide
HPV infection without detectable cytologic abnormalities	10 million	300 million
Low-grade dysplasia	1 million	30 million
High-grade dysplasia	300,000	10 million

- Virtually all cases of cervical cancer come from high-grade dysplasias.

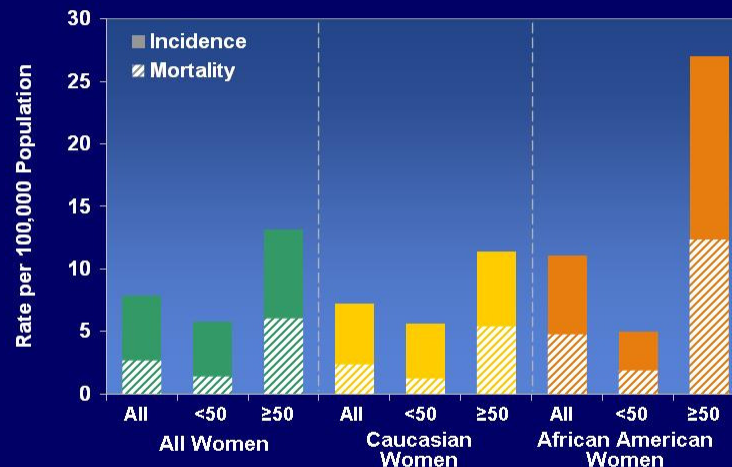
1. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22.

Oncogenic HPV Types Are a Necessary Cause of Cervical Cancer

- Infection with oncogenic HPV types is the most significant risk factor in cervical cancer etiology.¹
- Analysis of 932 specimens from women in 22 countries indicated prevalence of HPV DNA in cervical cancers worldwide = 99.7%.¹
- Specific oncogenic HPV types (16, 18, 31, 33, and 45) have been detected in 63%–97% of invasive cervical cancer cases worldwide.²

1. Walboomers JM, Jacobs MV, Manos MM, et al. *J Pathol*. 1999;189:12–19. 2. Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S. *Br J Cancer*. 2003;88:63–73.

Invasive Cervical Cancer: 2001 US Incidence and Mortality¹



- In 2003, US cases of cervical cancer ~12,200; deaths ~4,100²

1. National Cancer Institute. Bethesda, Md. National Cancer Institute, 2004. 2. American Cancer Society. Atlanta, Ga. American Cancer Society, 2003:1–48.

Mechanisms of HPV Transmission and Acquisition

- Sexual contact
 - Through sexual intercourse¹
 - Genital–genital, manual–genital, oral–genital^{2–4}
 - Genital HPV infection in virgins is rare, but may result from nonpenetrative sexual contact.²
 - Condom use may help reduce the risk, but it is not fully protective.²
- Nonsexual routes
 - Mother to newborn (vertical transmission; rare)⁵
 - Fomites (eg, undergarments, surgical gloves, biopsy forceps)^{6,7}
 - Hypothesized but not well documented

1. Kjaer SK, Chackerian B, van den Brule AJC, et al. *Cancer Epidemiol Biomarkers Prev.* 2001;10:101–106. 2. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. *Am J Epidemiol.* 2003;157:218–226. 3. Fairley CK, Gay NJ, Forbes A, Abramson M, Garland SM. *Epidemiol Infect.* 1995;115:169–176. 4. Herrero R, Castellsague X, Pawlita M, et al. *J Natl Cancer Inst.* 2003;95:1772–1783. 5. Smith EM, Ritchie JM, Yankowitz J, et al. *Sex Transm Dis.* 2004;31:57–62. 6. Ferenczy A, Bergeron C, Richart RM. *Obstet Gynecol.* 1989;74:950–954. 7. Roden RBS, Lowy DR, Schiller JT. *J Infect Dis.* 1997;176:1076–1079.

Risk Factors for HPV Infection

Women

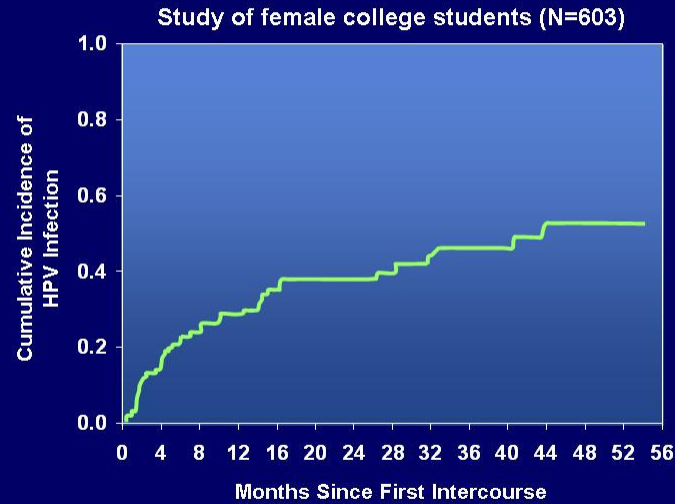
- Young age (peak age group 20–24 years of age)¹
- Lifetime number of sex partners²
- Early age of first sexual intercourse³
- Male partner sexual behavior³
- Smoking⁴
- Oral contraceptive use⁴
- Uncircumcised male partners⁵

Men

- Young age (peak age group 25–29 years of age)¹
- Lifetime number of sex partners⁶
- Being uncircumcised⁶

1. Insinga RP, Dasbach EF, Myers ER. *Clin Infect Dis.* 2003;36:1397–1403. 2. Burk RD, Ho GYF, Beardsley L, Lempa M, Peters M, Bierman R. *J Infect Dis.* 1996;174:679–689. 3. Murthy NS, Mathew A. *Eur J Cancer Prev.* 2000;9:5–14. 4. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. *Am J Epidemiol.* 2003;157:218–226. 5. Schiffman M, Castle PE. *Arch Pathol Lab Med.* 2003;127:930–934. 6. Svare EI, Kjaer SK, Worm AM, Osterlind A, Meijer CJLM, van den Brule AJ. *Sex Transm Infect.* 2002;78:215–218.

Infection From Time of First Sexual Intercourse



From Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: Incidence and risk factors in a cohort of female university students. *Am J Epidemiol.* 2003;157:218–226, by permission of Oxford University Press.

HPV Clearance

- In women 15–25 years of age, ~80% of HPV infections are transient.¹
 - Gradual development of cell-mediated immune response presumed mechanism²
- In a study of 608 college women, 70% of new HPV infections cleared within 1 year and 91% within 2 years.³
 - Median duration of infection = 8 months³
 - Certain HPV types are more likely to persist (eg, HPV 16 and HPV 18).

1. Meijer CJLM, Helmerhorst TJM, Rozendaal L, van der Linden JC, Voorhorst FJ, Walboomers JMM. *Histopathology.* 1998;33:83–86. 2. Schiffman M, Kjaer SK. *J Natl Cancer Inst Monogr.* 2003;31:14–19. 3. Ho GYF, Bierman R, Beardsley L, Chang CJ, Burk RD. *N Engl J Med.* 1998;338:423–428.

HPV Disease Progression¹

- In a study of women (N=899) 13–22 years of age positive for HPV DNA:
 - 260 (29%) were diagnosed with LSIL by cytology.
 - Probability of LSIL regression
 - 61% at 12 months' follow-up
 - 91% at 36 months' follow-up
 - Probability of progression to HSIL = 3%

1. Moscicki A-B, Shiboski S, Hills NK, et al. *Lancet*. 2004;364:1678–1683.

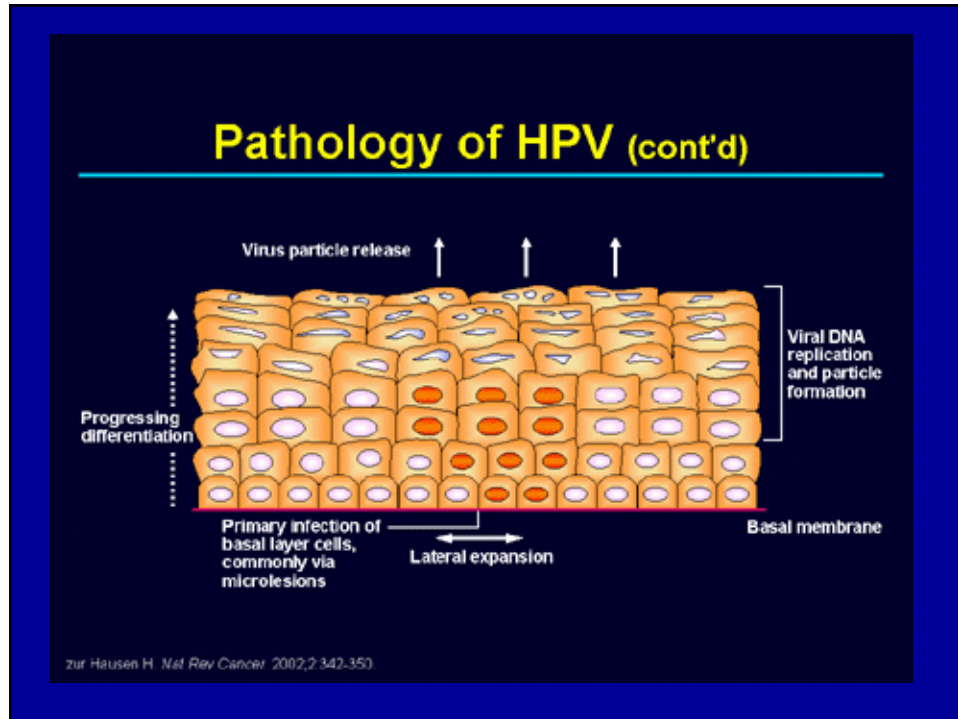
HPV Persistence

- Persistent infection: Detection of same HPV type two or more times over several months to 1 year¹
- Widely accepted that persistence of high-risk types of HPV is crucial for development of cervical precancer and cancer¹
- Other associated factors
 - Age (≥ 30 years)^{*,2}
 - Infection with multiple HPV types³
 - Immune suppression⁴
- Currently, there are no antivirals available to treat the underlying HPV infection.⁵

*May be partially confounded by duration of infection

1. Schiffman M, Kjaer SK. *J Natl Cancer Inst Monogr*. 2003;31:14–19. 2. Hildesheim A, Schiffman MH, Gravitt PE, et al. *J Infect Dis*. 1994;169:235–240. 3. Ho GYF, Burk RD, Klein S, et al. *J Natl Cancer Inst*. 1995;87:1365–1371.

4. Kobayashi A, Greenblatt RM, Anastos IK, et al. *Cancer Res*. 2004;64:6766–6774. 5. Stanley M. *J Natl Cancer Inst Monogr*. 2003;31:117–124.



Cervical cancer screening

- Current ACOG guidelines support annual screening beginning at age 21, may decrease frequency to every 3 years if repeatedly normal
- HPV testing may be used in conjunction with cervical cytology in women 30 years and older to help guide frequency of screening

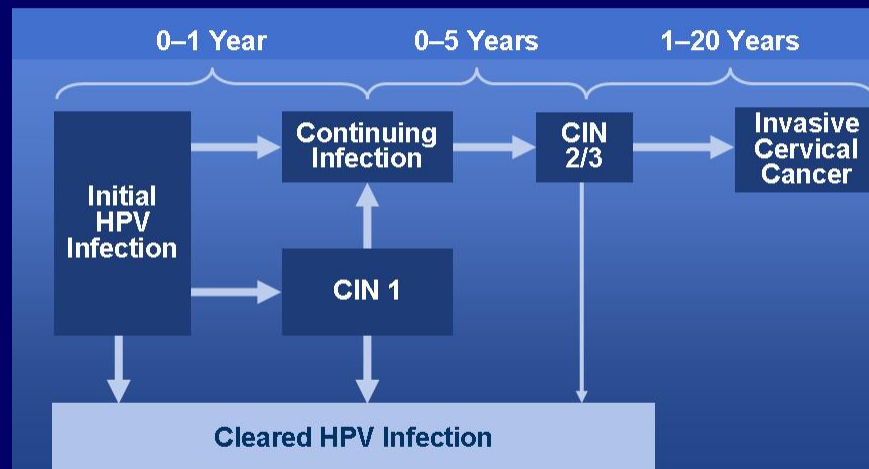
Cervical Cancer Prevention

- Cervical cancer screening (the Pap smear) has reduced cervical cancer deaths by 74% between 1955 and 1992
- In 2008,
 - 11,000 new diagnoses of cervical cancer in the U.S.
 - 3,900 deaths

Horner 2007, Ries 2007

<http://www.papsociety.org/drpap.html>

Natural History of HPV Infection and Potential Progression to Cervical Cancer¹

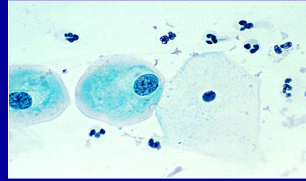


1. Pinto AP, Crum CP. *Clin Obstet Gynecol*. 2000;43:352-362.

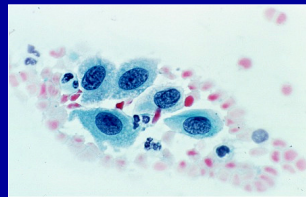
Dysplasia

High risk and low risk HPV types can cause dysplasia, for example:

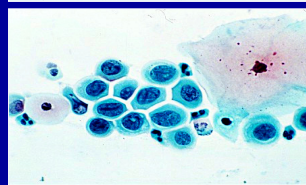
Atypical squamous cells (ASC)



Low grade squamous intraepithelial lesion (LSIL)



High grade squamous intraepithelial lesion (HSIL)



Synergy between HIV and STIs

Syphilis	↑↑↑↑↑	HIV	↑↑↑↑↑
GC/ CT/ Trich		HIV	↑↑
HPV	↑↑↑	HIV	

HIV and Pap Smears

- 30-60% of Pap smears from HIV positive women have cytological abnormalities (Larkin et al., 1999)
- 15-40% of these Pap smears exhibit dysplasia (Larkin et al., 1999)
- Women with HIV are more likely to have persistence of HPV and cervical dysplasia

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HIV Screening and Women's Health

Abnormal Pap Smears in HIV Positive Women

Genital Tract Neoplasia

Pap Smear Screening - WIHS Cohort followed for 3.5 years

	Cumulative Risk	
	HIV +	HIV -
Benign	33%	67%
Ascus	28%	23%
LGSIL	34%	8%
HGSIL	5%	3%
Cancer	0.4%	0%

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HIV Screening and Women's Health

Cervical Neoplasia

1. Cervical cancer is an AIDS defining illness
 1. In a study of 2,015 HIV-infected women and 577 seronegative controls, 58% of HIV-infected women had HPV as compared with the seronegative controls of 26%
2. In HIV positive women, dysplasia is associated with more extensive cervical involvement and is more likely to involve other sites in the lower genital tract

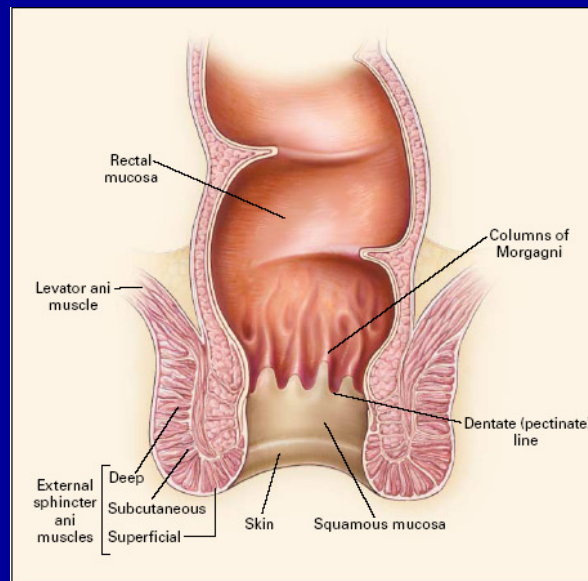
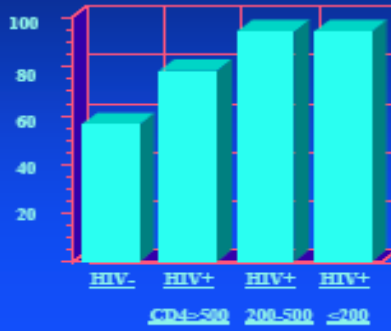
25

HIV Screening and Women's Health

Anal and Cervical Cancer Incidence

- Cervical cancer prior to cervical cytology 40-50/100,000
- Cervical cancer currently 8/100,000
- Anal cancer among HIV- MSM 13-35/100,000
- Anal cancer twice as high among HIV+ MSM 70-??/ 100,000

Percent with anal HPV infection



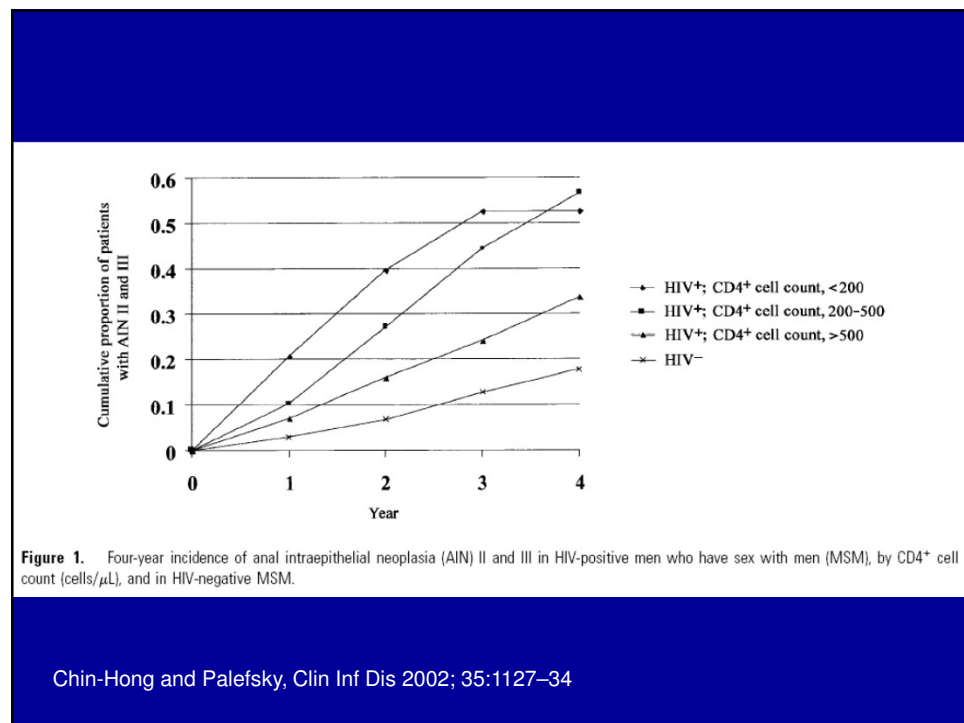
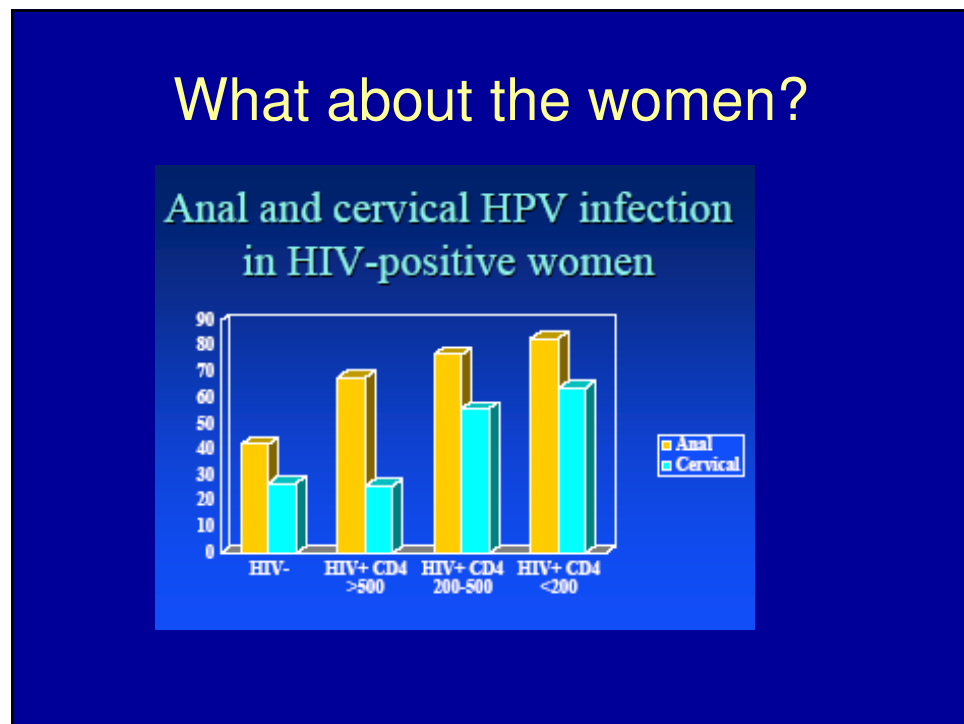


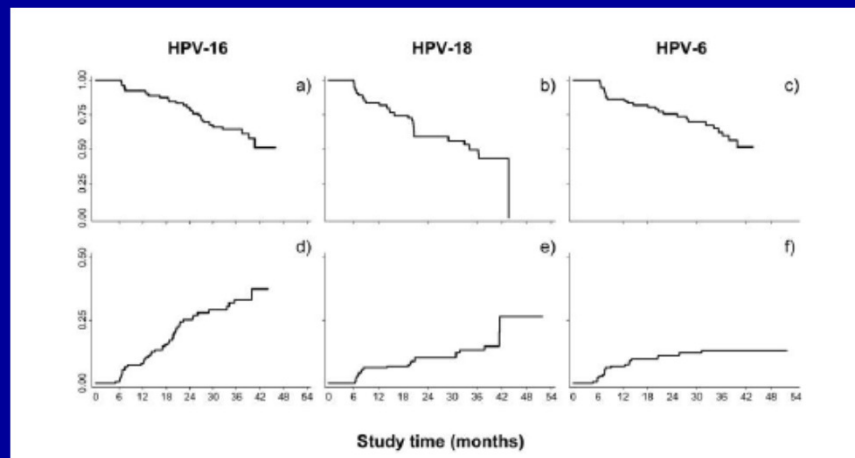
Table 1. Detailed histological grades for paired cytological specimens.

Cytological category	No. of specimens	Histological grade, no. (%) of specimens				
		Normal	AIN level 1	AIN level 2	AIN level 3	SCC
Normal	19	11 (58)	7 (37)	0 (0)	1 (5)	0 (0)
ASCUS	30	11 (37)	7 (23)	5 (17)	7 (23)	0 (0)
LSIL	72	10 (14)	36 (50)	13 (18)	13 (18)	0 (0)
HSIL	32	1 (3)	7 (22)	4 (13)	18 (57)	2 (6)
Total	153	33	57	22	39	2

NOTE. Histological specimens are high-resolution anoscopy-guided biopsy specimens that were obtained during the same examination as the anal Papanicolaou (Pap) smear; if biopsy was not performed at this time, histological specimens represent surgical pathology findings, if they were recorded within 3 months of the anal Pap smear. AIN, anal intraepithelial neoplasia; ASCUS, atypical squamous cells of uncertain significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; SCC, anal squamous cell carcinoma.

Panther CID 2004:38 (15 May)

HPV clearance in HIV+ individuals



Pokomandy 2009

Genital warts

- Low risk for cancer but still problematic

HPV and Anogenital Warts



Perianal warts

- HPV 6 and 11 responsible for >90% of anogenital warts¹
- Peak prevalence²
 - Women 20–24 years of age (6.2/1,000 person years)
 - Men 25–29 years of age (5.0/1,000 person years)
- Clinically apparent in ~1% of sexually active US adult population³

1. Jansen KU, Shaw AR. *Annu Rev Med.* 2004;55:319–331. 2. Insinga RP, Dasbach EF, Myers ER. *Clin Infect Dis.* 2003;36:1397–1403. 3. Koutsky L. *Am J Med.* 1997;102:3–8.

HPV and Anogenital Warts (cont'd)



Genital warts

- Infectivity >75%¹
- Up to 40% spontaneously remit.²
- Treatment can be painful and embarrassing.³
- Topical and surgical therapies are available for genital warts.⁴
- Recurrence rates vary greatly.⁴
 - As low as 5% with podofilox or laser treatment
 - As high as 65% with other treatments

1. Soper DE. In: Berek JS, ed. *Novak's Gynecology*. 13th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2002:453–470. 2. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis*. 2002;35(suppl 2):S210–S224. 3. Maw RD, Reitano M, Roy M. *Int J STD AIDS*. 1998;9:571–578. 4. Kodner CM, Nasraty S. *Am Fam Physician*. 2004;70:2335–2342.

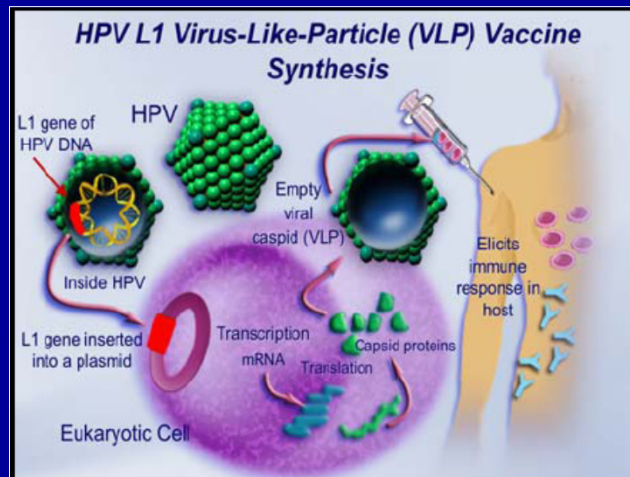
Treatment options

- Local TCA, podophyllin
- Imiquimod 5%
- Liquid nitrogen
- Infrared laser coagulation
- Surgery

What can be done??

VACCINATE!!

And do it soon



HPV vaccines

- Quadrivalent
 - Merck 6,11,16,18 *Gardasil*
 - FDA approved for men and women 9-26
- Bivalent
 - GSK 16,18 *Cervarix*
 - FDA approval for women 10-25
- Both are 3 series and highly immunogenic

HPV vaccines

cont'd

- None offer therapeutic benefit once infected
- Not approved for use in men although studies ongoing
- Not protect against all high risk serotypes-
 - ⇨ Sero-replacement ?

HPV Vaccine

- HPV vaccination prevents
 - HPV infection
 - Cervical cancer and its precursors
 - Genital warts

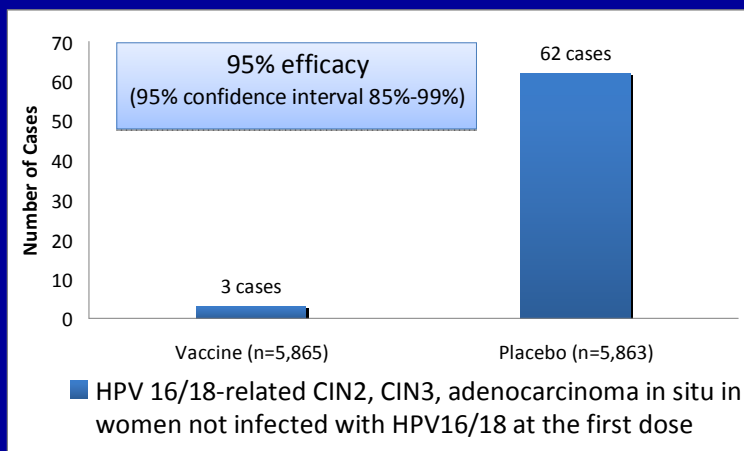
Rationale for Recommended Ages of Vaccination

- Vaccination should occur prior to HPV infection
- 6.2% of adolescents have sexual intercourse before 13 yo

HPV Vaccines Clinical Trials

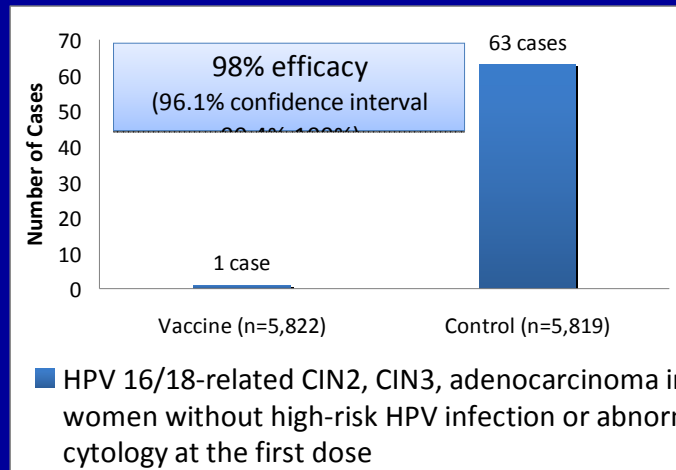
- Clinical trials with
 - >50,000 young women
 - ~4,000 young men
- Randomized, controlled

Quadrivalent Vaccine Efficacy Against Abn. Histology



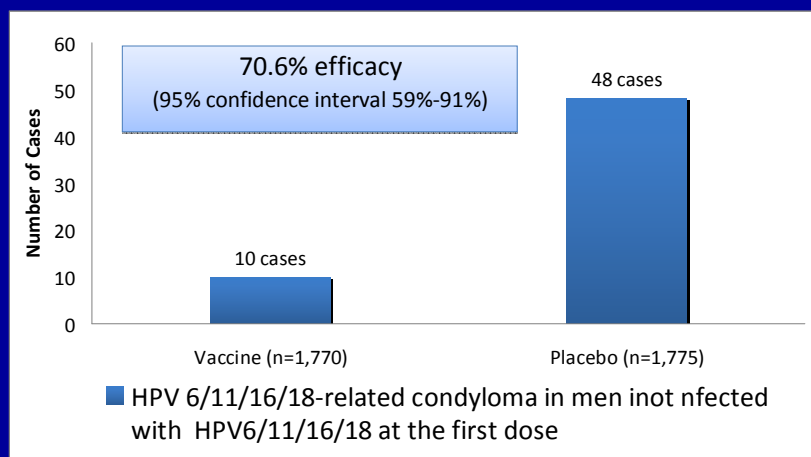
Future II, 2007

Bivalent Vaccine Efficacy Against Abnormal Histology



Paavonen 2009

Quadrivalent Vaccine Efficacy Against Warts in Men



<http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM190977.pdf>

Safety Post-Licensing

- 23 million doses of the quadrivalent vaccine administered since 2006
- VAERS
 - Vaccine adverse event reporting system

Slade, 2009

Nonserious VAERS Reports

- 94% of VAERS reports are classified as nonserious
- The most common events were
 - Syncope
 - Pain at injection site
 - Dizziness
 - Nausea
 - Headaches

Serious Events Reported to VAERS

- 6% of VAERS reports classified as serious
 - Death (32 reported)
 - 26 confirmed deaths
 - No clustering
 - No association with vaccine
 - e.g., Diabetes, viral illness, illicit drug use, heart failure
 - 2 reports of unusual neurological illnesses
 - CDC/FDA review concluded that these events do not appear to be causally linked to the vaccine

Age of Vaccination in Females

- Bivalent (HPV2, Cervarix) and Quadrivalent (HPV4, Gardasil)
- Target population is 11 to 12 year olds
- 9 to 10 year olds can be vaccinated at provider discretion
- 13 to 26 year olds should be vaccinated
 - Follow recommended dosing intervals in 13-26 yo, not the minimum recommended intervals

<http://www.cdc.gov/vaccines/recs/provisional/downloads/hpv-vac-dec2009-508.pdf>

HPV Vaccination in Males

- **Quadrivalent vaccine only (HPV4, Gardasil)**
- “may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact”

<http://www.cdc.gov/mmwr/PDF/wk/mm5920.pdf>

Precautions

- Syncope
 - Due to vasovagal reactions
 - Because of the risk of head injury from falling, sit or lie for 15 minutes after vaccination

Vaccine and Pregnancy

- HPV vaccines are not recommended in pregnancy
 - Ask about chance of pregnancy
 - Pregnancy test only required if indicated by patient's history
- Neither vaccine has been shown to be causally associated with adverse outcomes in pregnant women or fetuses

Contraindications

- Immediate hypersensitivity to yeast
- Any vaccine component

HIV and HPV vaccination

- One completed study of safety and efficacy in HIV+ men.
- Safe
- Very immunogenic but less so than HIV-
- Unclear if clinically significant
- Currently enrolling HIV+ females for similar study

Still Give the Vaccine

- Regardless of abnormal Pap smears
- Regardless of genital warts
- Breast-feeding
- Immunocompromised
 - Vaccine not infectious
 - Immunocompromised patients may be at increased risk from HPV associated cancers
- Concomitantly with other vaccines

Even Though You're Vaccinated

- Cervical cancer screening should continue regardless of vaccination status
 - Patients may already be infected with vaccine-HPV types before vaccination
 - Nonvaccine types can still cause dysplasia, precancersous lesions, and cancer
- Condoms are still needed to prevent other STIs

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