

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

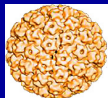
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Learning Objectives

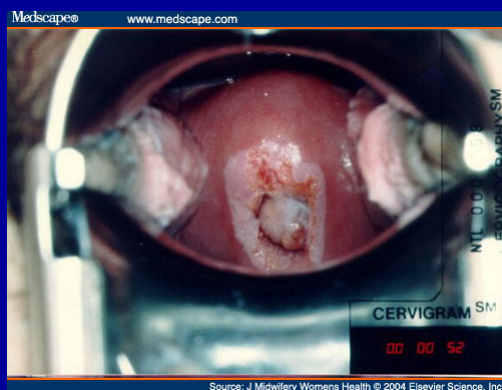
At the end of this session, the participant will be able to:

- Explain the spectrum of disease associated with HPV
- Describe the natural history of HPV infection
- Identify patients who would benefit from and strategies to incorporate HPV vaccination into clinical practice.
- Develop responses to questions that patients ask about HPV vaccine.



HPV Disease Burden in the US

- Anogenital HPV is the most common sexually transmitted infection in the US
- Infection without detectable cytologic abnormalities
 - Estimated 10-20 million currently infected
 - ~ 6.2 million new infections/year
- Common among adolescents and young adults
- Men appear to have a higher prevalence of HPV infections as compared to women









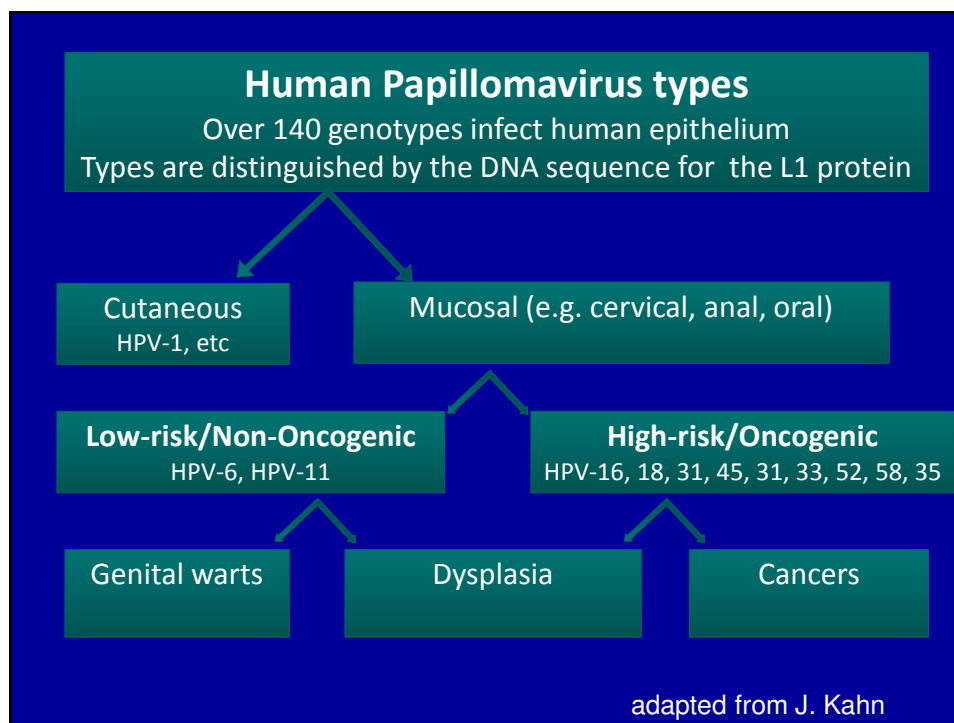
Epidemiology of HPV

- 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**

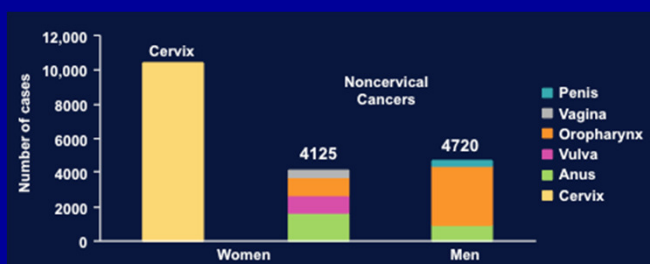
HPV in the US

- An estimated 32,000 cases of cancers in men and women were attributable to HPV infection in 2009
 - Cervix – Vagina – Vulva – Penis
 - Oral Cavity – Head and Neck
 - Anal canal
- Anogenital warts are the most common outcome of HPV with 205 cases per 100,000 diagnosed annually

Giuliano et al, *Lancet* online March 1, 2011.



Annual Burden of HPV-Associated Cancers Among Men and Women



- The burden of noncervical cancers ~ burden of cervical cancers
- Burden of noncervical cancers is equal among men and women
- Oropharyngeal cancers contribute to a substantial burden of HPV-associated cancers among men (75%) and a considerable burden of non-cervical HPV-associated cancers among women (26%)

Gillison ML, et al. *Cancer*. 2008;113,S10:3036-3046

HPV and Cancer¹

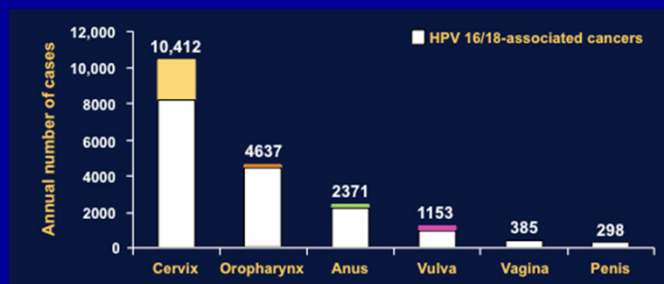
Cancer	% Associated With Certain HPV Types
Cervical*	≥95%
Vaginal*	50%
Vulvar*	≥50%
Penile	50%
Anal	>70%
Oropharyngeal	20%
Nonmelanoma skin/cutaneous squamous cell	90%†

*Includes cancer and intraepithelial neoplasia

†Immunocompromised patients

1. Gonzalez Iturraraga MA, Stankovic R, Sorli R, Trevisan G. *Acta Dermatovenereol*. 2002;11:1–8.

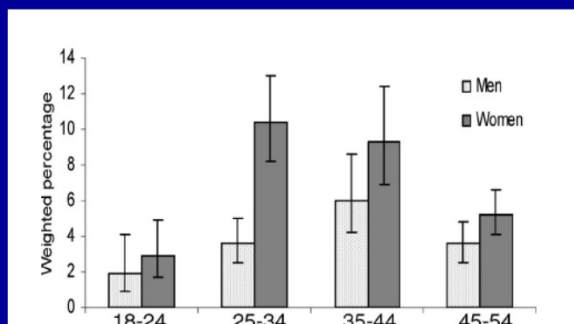
Annual Burden of HPV-Associated Cancers In the United States



- Cancers of the oropharynx and anus that occur in men and women account for a substantial proportion of HPV-associated cancers in the US.
- The majority of HPV-associated cancers in the US are attributable to HPV types 16 and 18.

Gillison ML, et al. *Cancer*. 2008;113.S10:3036-3046

Genital Warts in the U.S. Population NHANES, 1994-2004



Percentage of sexually active persons 18-59 years of age who reported ever having a diagnosis of genital warts

5.6% of sexually active 18-59 year olds reported having been diagnosed with genital warts

Dinh et al. *STD*. 2008; 35: 357-360.

HPV-Associated Conditions

Estimated Attributed %

HPV 16, 18

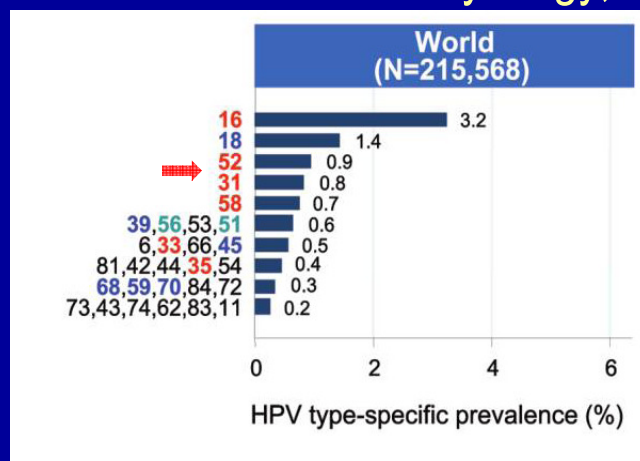
- Cervical cancer 70%
- High grade cervical abnormalities 50%
- Low grade cervical abnormalities 30%
- Anal cancer ~70%
- Vulvar/Vaginal/Penile ~40%
- Head and neck cancers ~10%~25%

HPV 6, 11

- Low grade cervical abnormalities 10%
- Genital warts 90%
- Recurrent respiratory papillomatosis (RRP) 90%

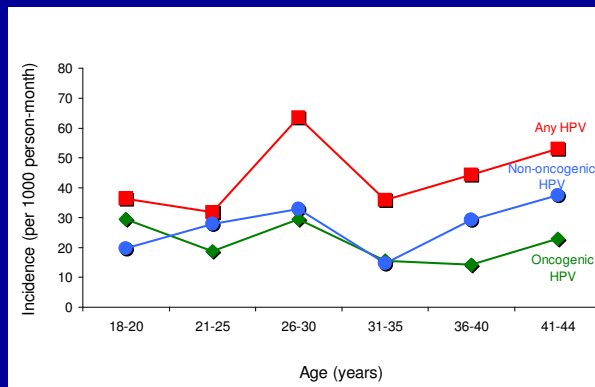
Clifford, *BJ Ca*. 2003; Munoz, *Int J Cancer*. 2004; Brown *J Clin Micro*. 1993; Carter *Cancer Res*. 2001;
Clifford, *Cancer Epi Biomarkers Prev*. 2005; Gissman, *Proc Natl Acad Science*. 1983;
Kreimer, *Cancer Epidemiol Biomarkers Prev*. 2005; D'Souza, *NEJM*. 2007

Type-Specific HPV Prevalence Among Women With Normal Cervical Cytology, Worldwide



Type-specific HPV prevalence for most frequent HPV types among women with normal cervical cytology.
Bruni et al. *JID* 2010;202:1789-1799. Meta-analysis data from WHO

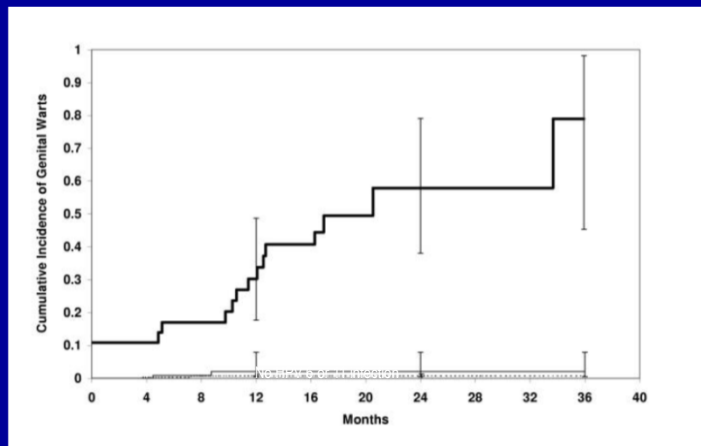
Age-specific HPV Incidence in Men



Thanks to Dr Stephen Goldstone for the use of this slide

Giuliano AR et al. *JID*: 2008

Time to Development of Genital Warts Among Men Who Acquire HPV Infection



By 2 years, 58% with detected HPV6 or 11 develop clinical warts

Arima Y, et al. *JID* 2010;202:1181-1184

Oral Cancers in Males

- Most oral cancers are associated with alcohol and tobacco use
- A subset of oral cancers is associated with HPV and sexual behaviors associated with HPV acquisition
 - Typically in oropharynx, especially in the tonsils
- The incidence of these HPV-associated cancers is increasing in the general population in contrast to oral cancers associated with tobacco and alcohol use, which are declining
- Oral HPV infection is much less common in adults than anogenital HPV infection, however risk factors associated with sexual behavior are associated with oral HPV detection

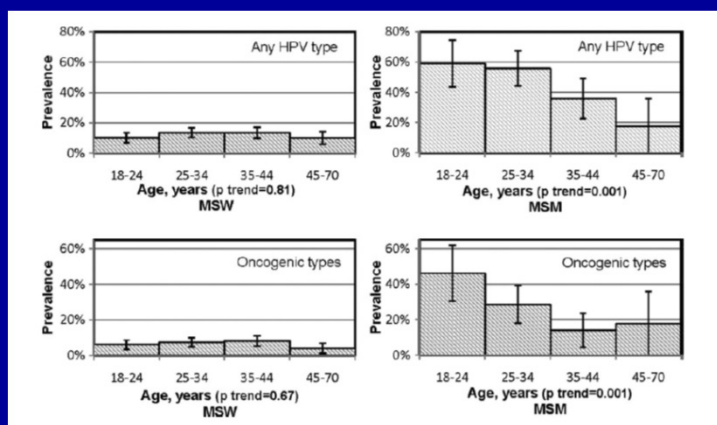
Palefsky, JM *J Adol Health*. 2010;46, S12-19

HPV in MSM

- Greater burden of HPV-related outcomes including genital warts, anal precancers and anal cancers
 - Anal cancer: 2 per 100,000 in men and 35 per 100,000 in HIV-MSM
 - Currently no routine recommendations for anal cancer screening
 - Immunization of females would likely have minimal impact
 - Anticipated high acceptability of vaccine

Hong PV et al. *Clin Infect Dis* 2002; Johnson LG et al. *Cancer* 2004; Simathurai et al. *Sex Transm Inf* 2009

Prevalence of Anal HPV Infection Among Men (MSW and MSM)



Nyitray AG et al. *JID* 2011;203:49-57

Natural History of HPV in Females

- HPV Clearance
 - Approximately 70% of new infections clear within one year, 91% within 2 years
 - Most clearance is in the first 6 months
- HPV Persistence
 - Infection detected at more than one visit (usually 4-6 months apart)
 - Most important predictor of high grade cervical cancer precursors

Ho et al., NEJM 1998; Moscicki et al., J Pediatr 1998; Franco et al., JID 1999; Molano et al., Am J Epidemiol 2003

Natural History of HPV in Males

- Natural history of HPV in men is different than in women
 - High infection and low disease rates in men
 - Male clearance occurs within a shorter time
 - Natural history of oncogenic HPV infection in men should not be extrapolated to that of women
 - Treatment of genital HPV disease in men does not affect the natural history or recurrence of CIN in female partners

J Monsonego. *Lancet* online March 1, 2011.

When to Vaccinate?

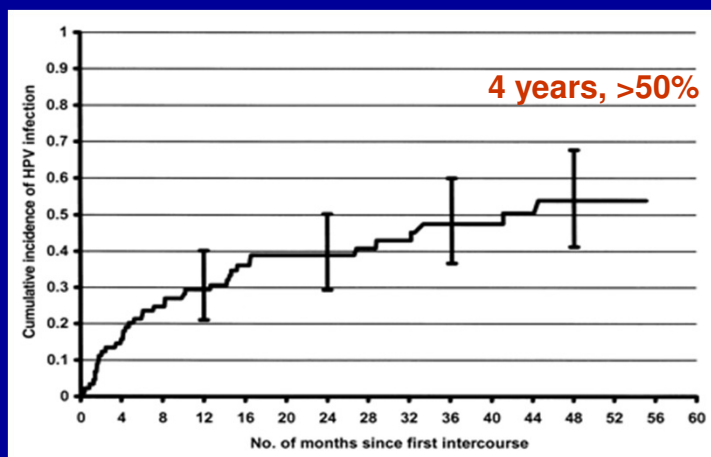
Before exposure to HPV

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.

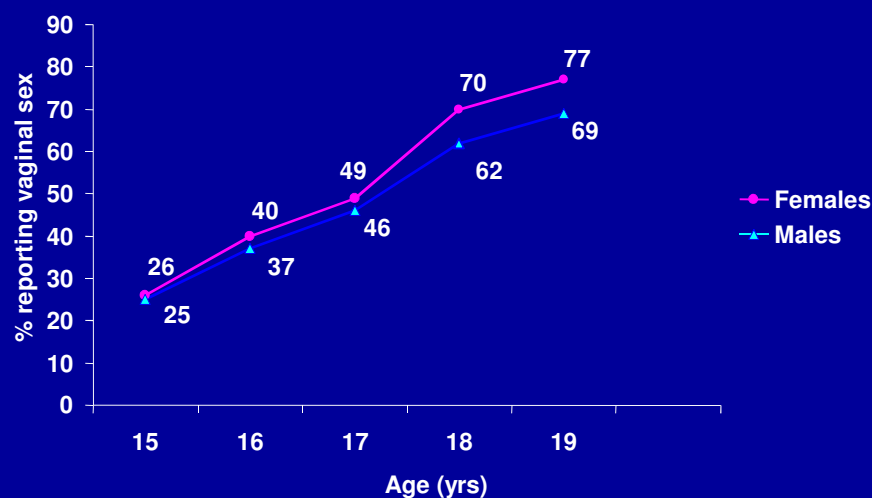
Infection From Time of First Sexual Intercourse Months After Sexual Initiation



603 Female college students; HPV negative at outset

Winer, et al. *Am J Epidemiol.* 2003.

Percentage of Adolescents Who Have Had Vaginal Sex, by Gender and Age, National Survey of Family Growth (NSFG), 2002



Mosher, et al., 2005; Vital and Health Statistics: No. 362

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

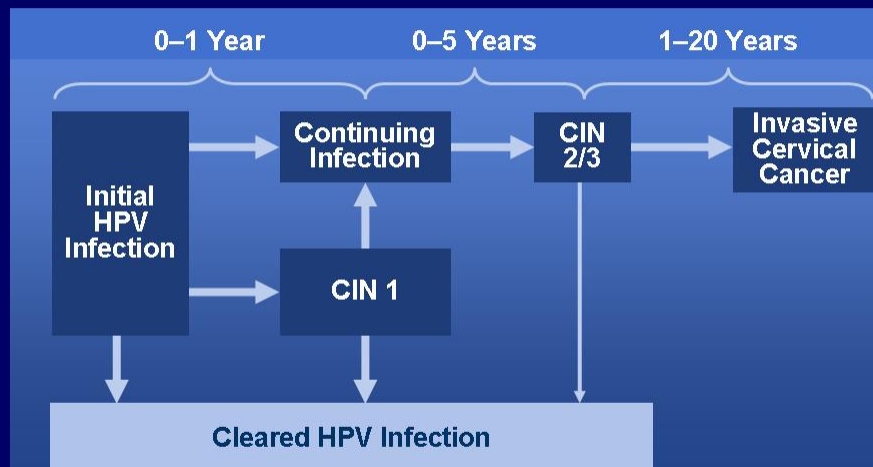
- Persistent infection: Detection of same HPV type two or more times over several months to 1 year¹
- Widely accepted that persistence of high-risk types of HPV is crucial for development of cervical precancer and cancer¹
- Other associated factors
 - Age (≥ 30 years)^{*,2}
 - Infection with multiple 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.

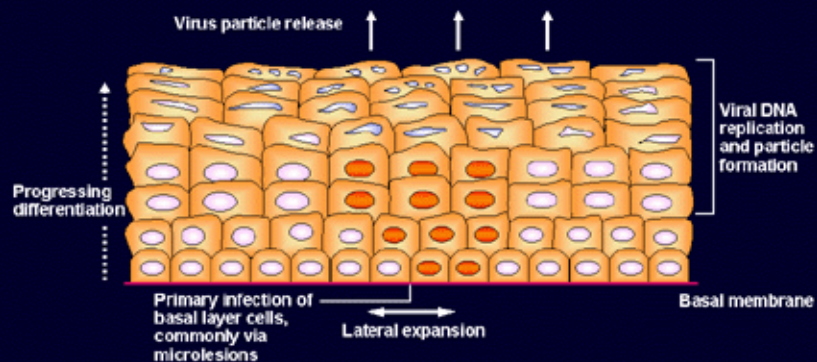
4. Kobayashi A, Greenblatt RM, Anastos K, et al. *Cancer Res*. 2004;64:6766–6774. 5. Stanley M. *J Natl Cancer Inst Monogr*. 2003;31:117–124.

Natural History of HPV Infection and Potential Progression to Cervical Cancer¹



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

Pathology of HPV (cont'd)



zur Hausen H. *Nat Rev Cancer*. 2002;2:342–350.

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

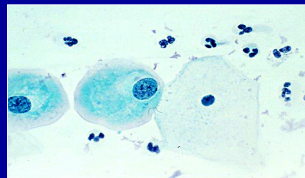
Horner 2007, Ries 2007

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

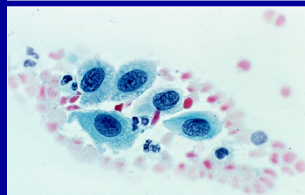
Dysplasia

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

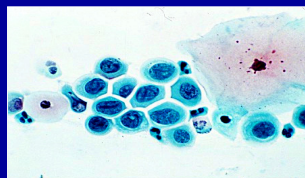
Atypical squamous cells (ASC)



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

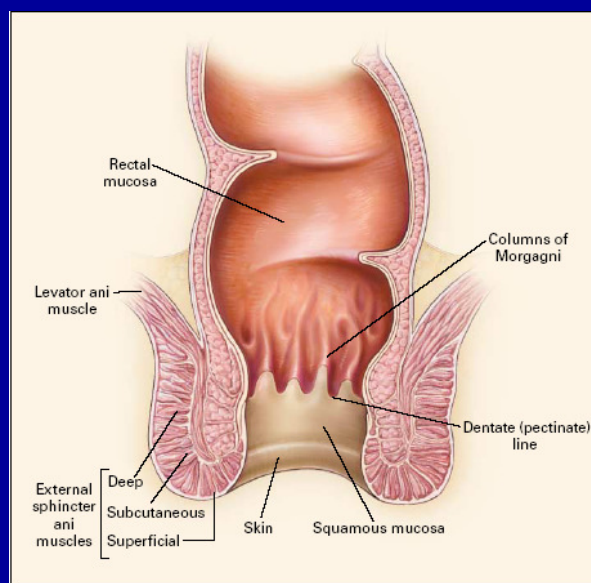
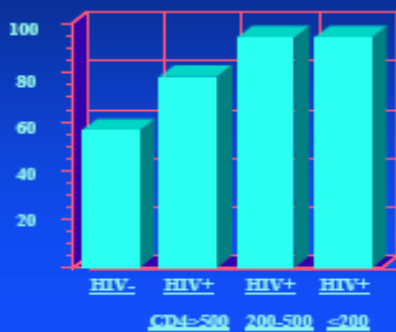
Pap Smear Screening - WIHS Cohort followed for 3.5 years

	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

Percent with anal HPV infection



What about the women?

Anal and cervical HPV infection in HIV-positive women

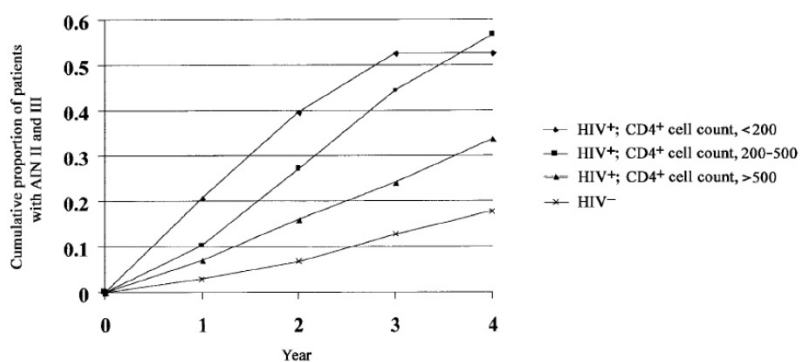
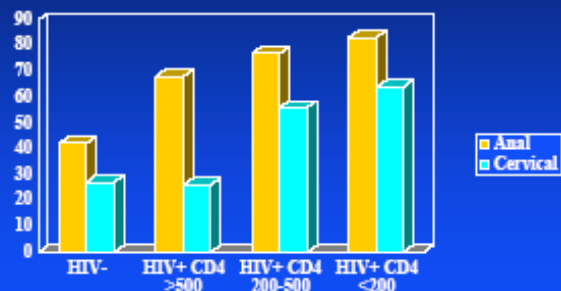
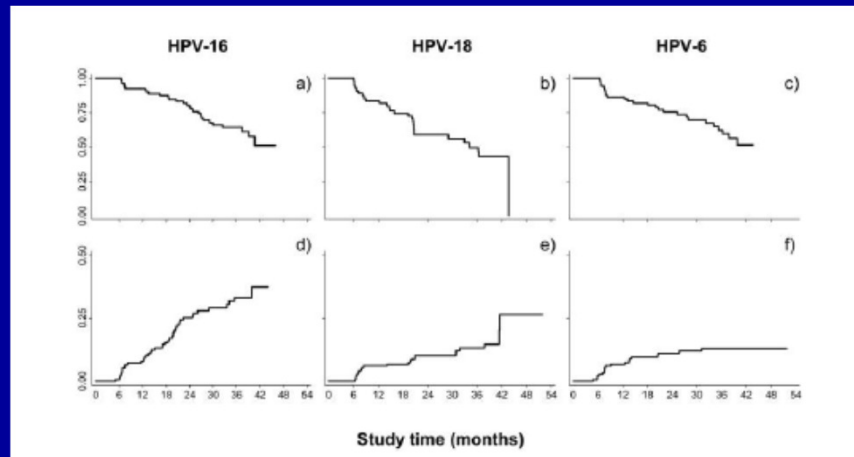


Figure 1. Four-year incidence of anal intraepithelial neoplasia (AIN) II and III in HIV-positive men who have sex with men (MSM), by CD4⁺ cell count (cells/ μ L), and in HIV-negative MSM.

Chin-Hong and Palefsky, Clin Inf Dis 2002; 35:1127-34

HPV clearance in HIV+ individuals

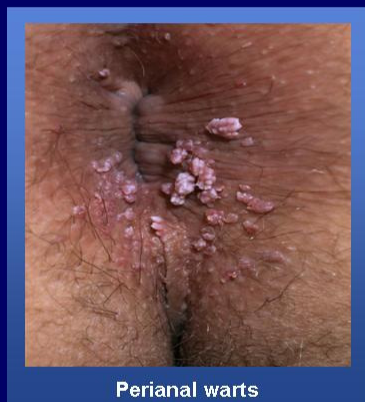


Pokomandy 2009

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.

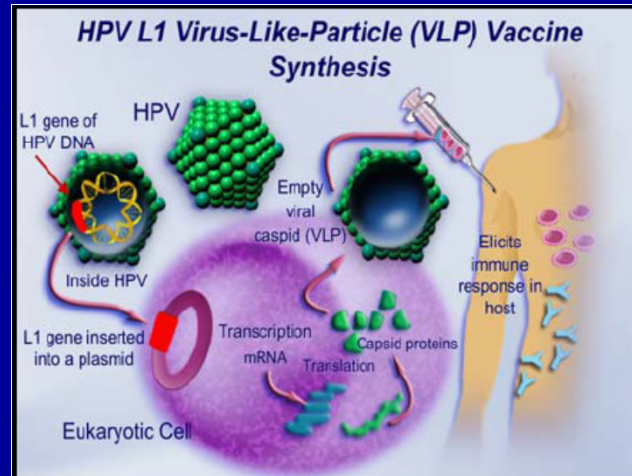
Treatment options

- 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

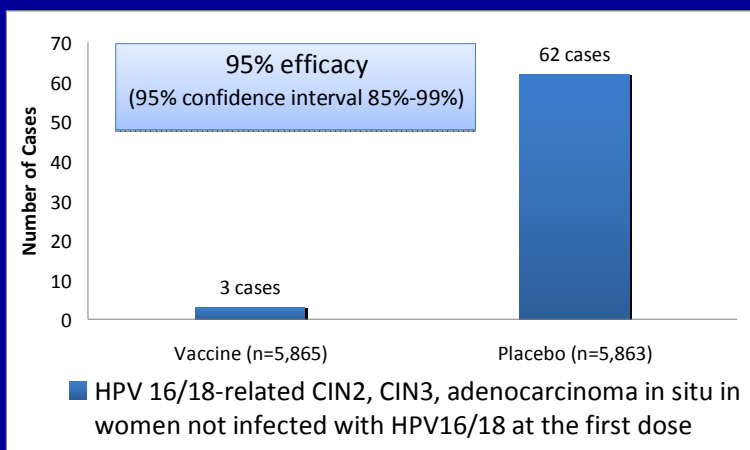
Rationale for Recommended Ages of Vaccination

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

HPV Vaccines Clinical Trials

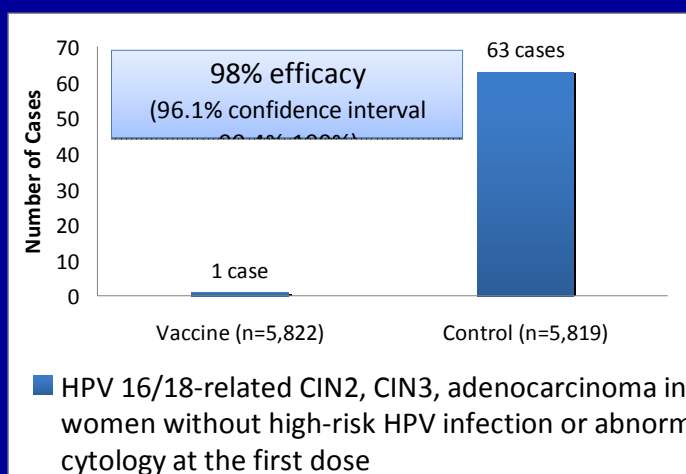
- Clinical trials with
 - >50,000 young women
 - ~4,000 young men
- Randomized, controlled

Quadrivalent Vaccine Efficacy Against Abn. Histology



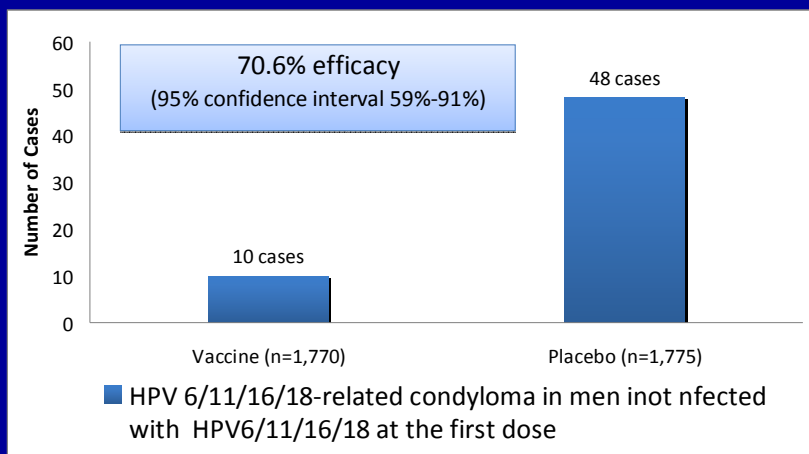
Future II, 2007

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

There are no contraindications
to simultaneous administration
of any vaccines

It is not necessary to restart the series of any routine vaccine due to extended intervals between doses

Pregnancy testing is
not required
before administration of any vaccine

Use clinical judgment

A vaccine not given
is
100% not effective

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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