

Human Papilloma Virus and Disease

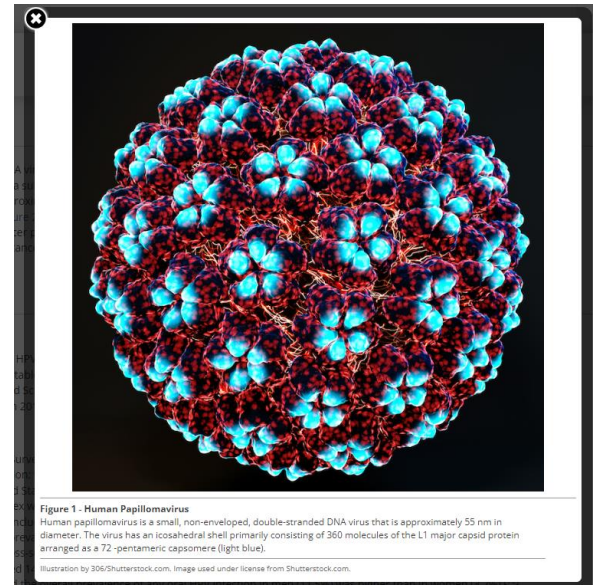
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February 28th 2024

Learning Objectives

- Describe the epidemiology of HPV in the USA
- Appreciate the risks for HPV infection
- Understand the disease manifestations of HPV
- Implement screening guidelines for anal & cervical cancer
- Explain the role of vaccines in prevention of HPV disease

Impact of HPV in the U.S.

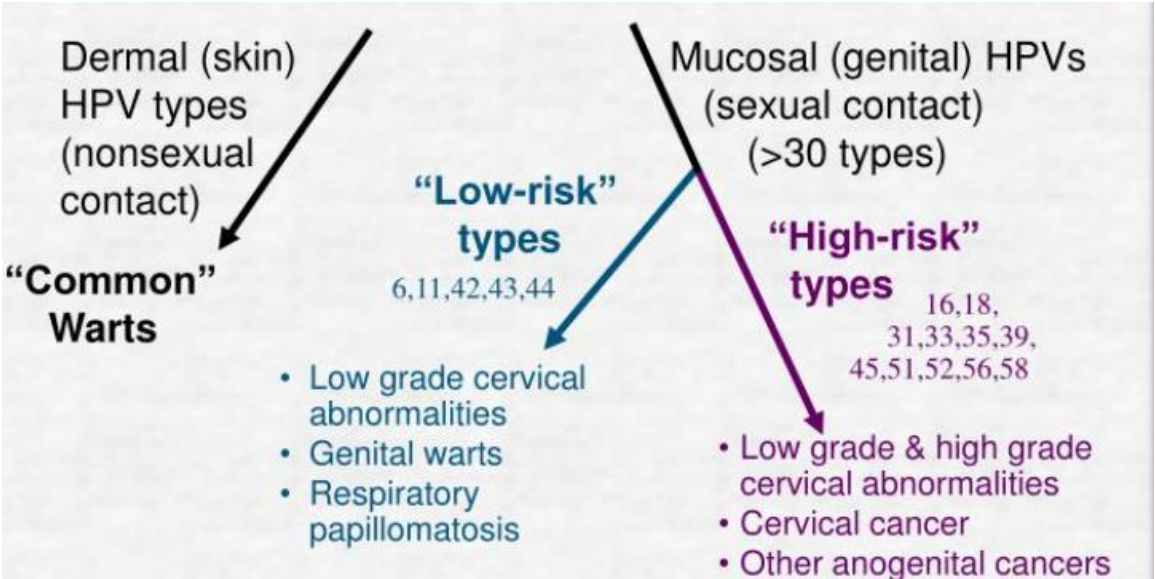
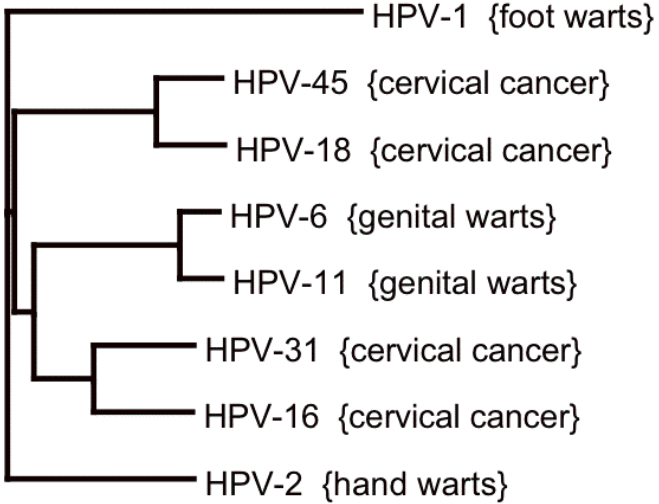
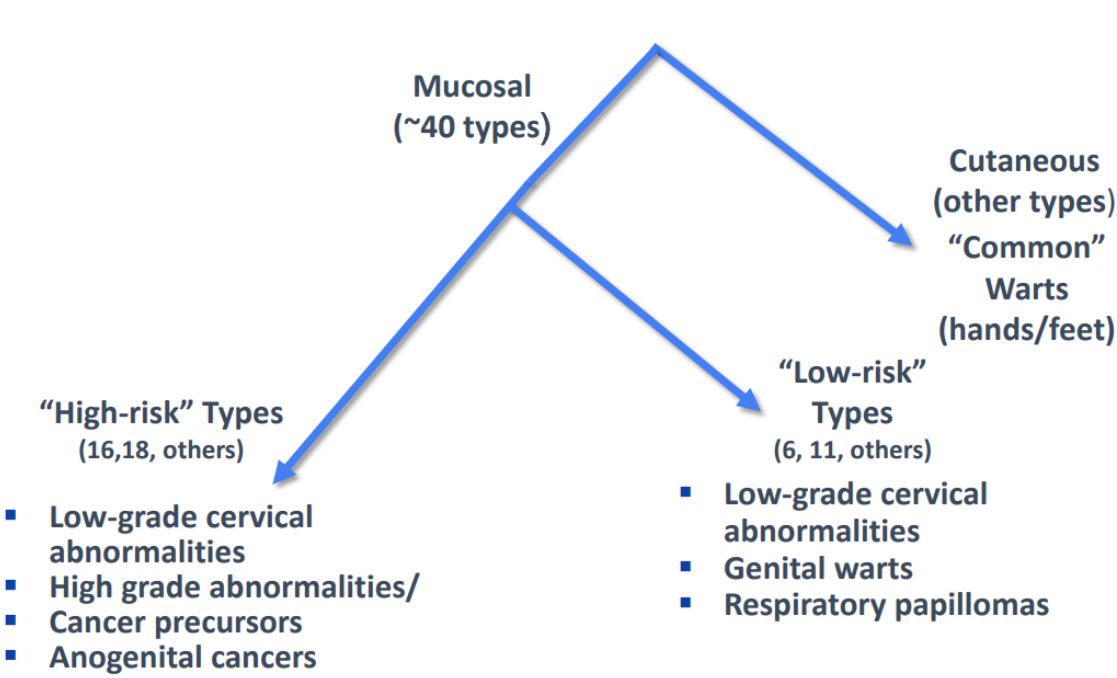
- Prevalence of 79 million persons in the U.S.
- Incidence (new cases) of 14 million cases each year
- HPV is the most common STI
 - Most sexually active people will become infected
- Most persons have no symptoms after infection



“HPV is so common that almost every person who is sexually-active will get HPV at some time in their life if they don’t get the HPV vaccine.”

– Centers for Disease Control and Prevention

HPV types & disease

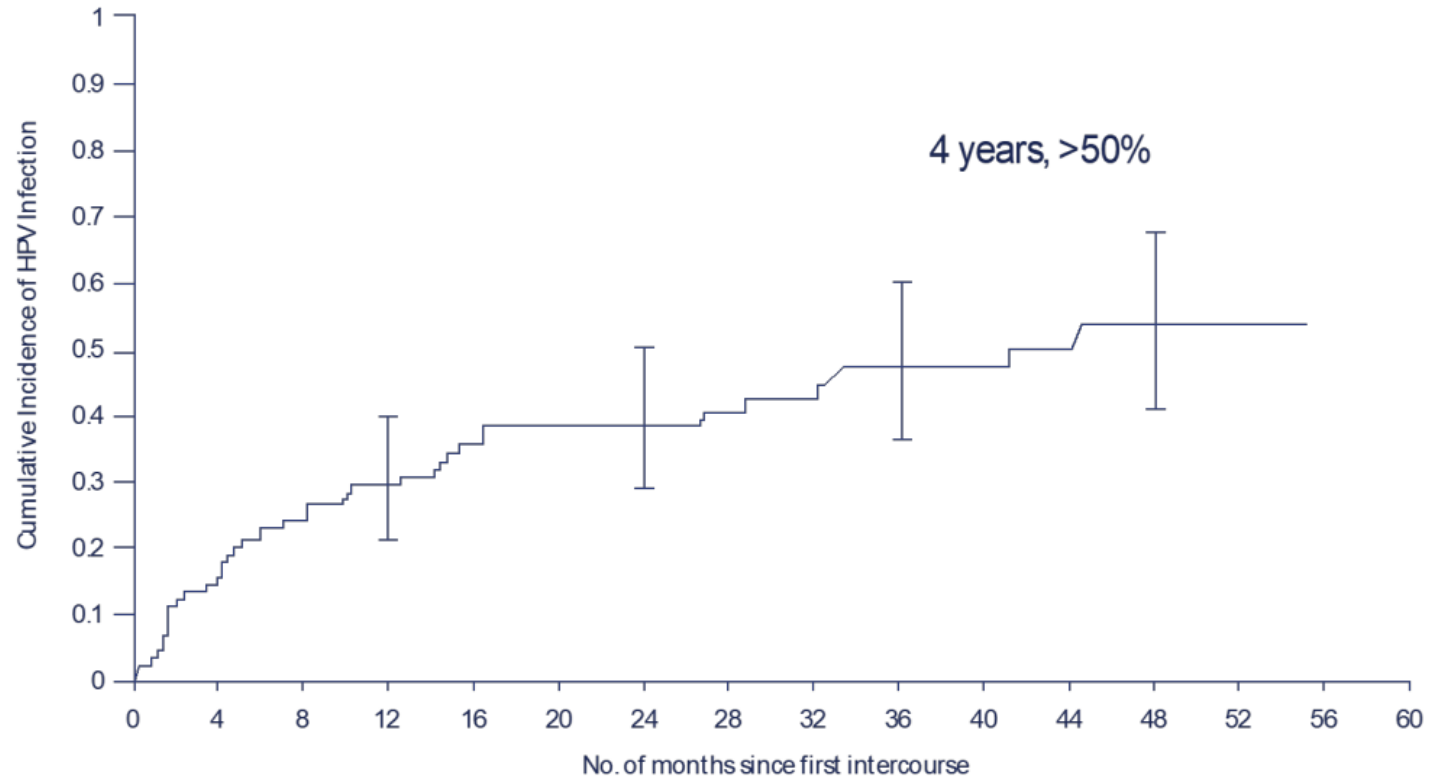


Patient FAQs: Did my partner give me HPV?

- You can get HPV by having vaginal, anal, or oral sex with someone who has the virus. It is spread mainly through vaginal or anal sex
- HPV types that can cause genital warts are not the same as the types of HPV that can cause cancers.
- HPV can be passed even when an infected person has no signs or symptoms.
- You can get HPV if you have had sex with only one person.
- You also can develop symptoms years after you have sex with someone who has HPV. This makes it hard to know when you first became infected
- Non-sexual transmission [skin warts]
- Digital transmission & self –inoculation

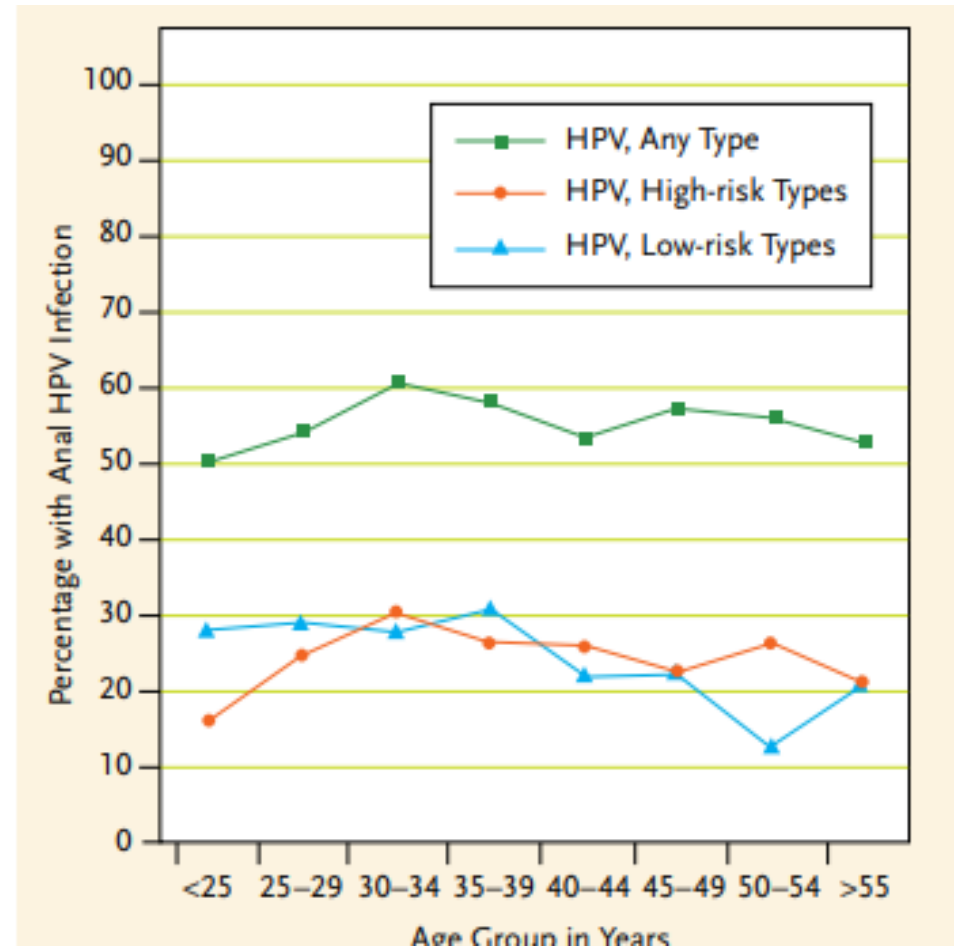
Risks for HPV Infection

Cumulative incidence of HPV infection after sexual initiation



HPV infection in sexually active HIV negative MSM

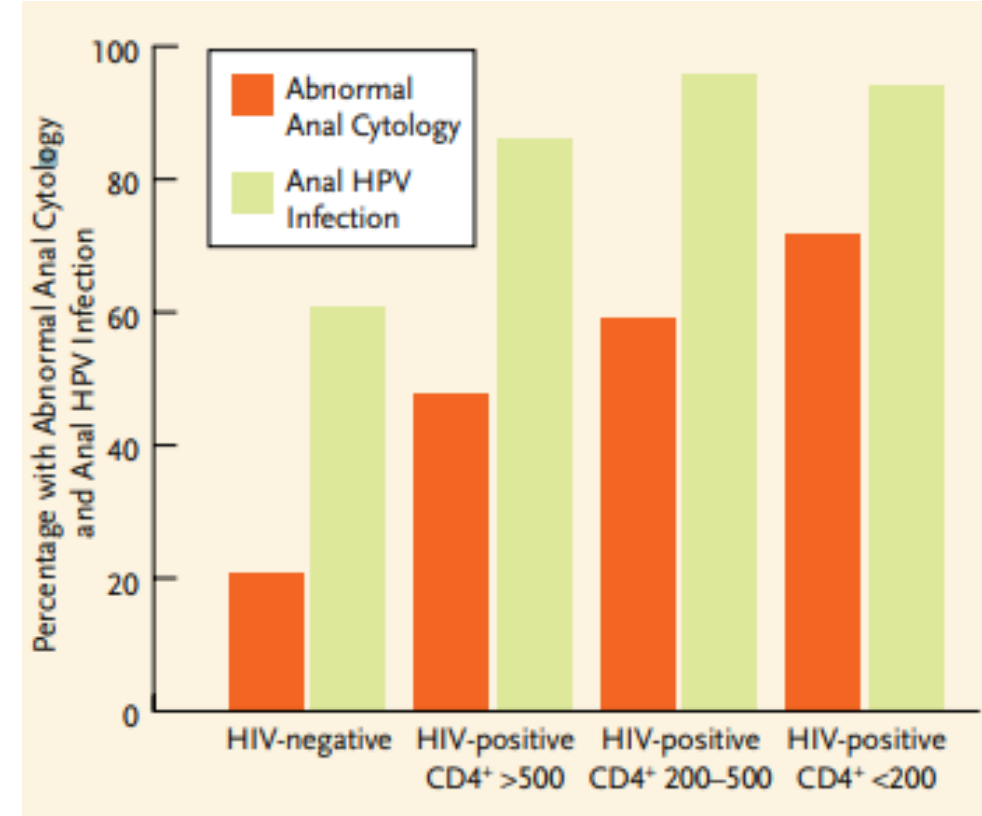
- Persistence of anal HPV infection in HIV negative MSM seems to be different than in biologic females.
- Prevalence of HPV remains high at (50- 60 %) in MSM through out life
- Biologic females the prevalence of HPV peaks in age 20 and seems to decline by age 30



University of Chicago Press

Patient FAQs. Does HPV cause cancer?

- HPV causes cancers, including oral cancer, cervical cancer & anal cancer
- No way to know which people who have HPV will develop cancer
- Takes decades in most people to develop cancer unless have weak immune system such as HIV
 - Prevalence of AIN [anal cytology] in HIV + vs HIVnegative MSM
- Weak immune systems (including those with HIV/AIDS) may be less able to fight off HPV

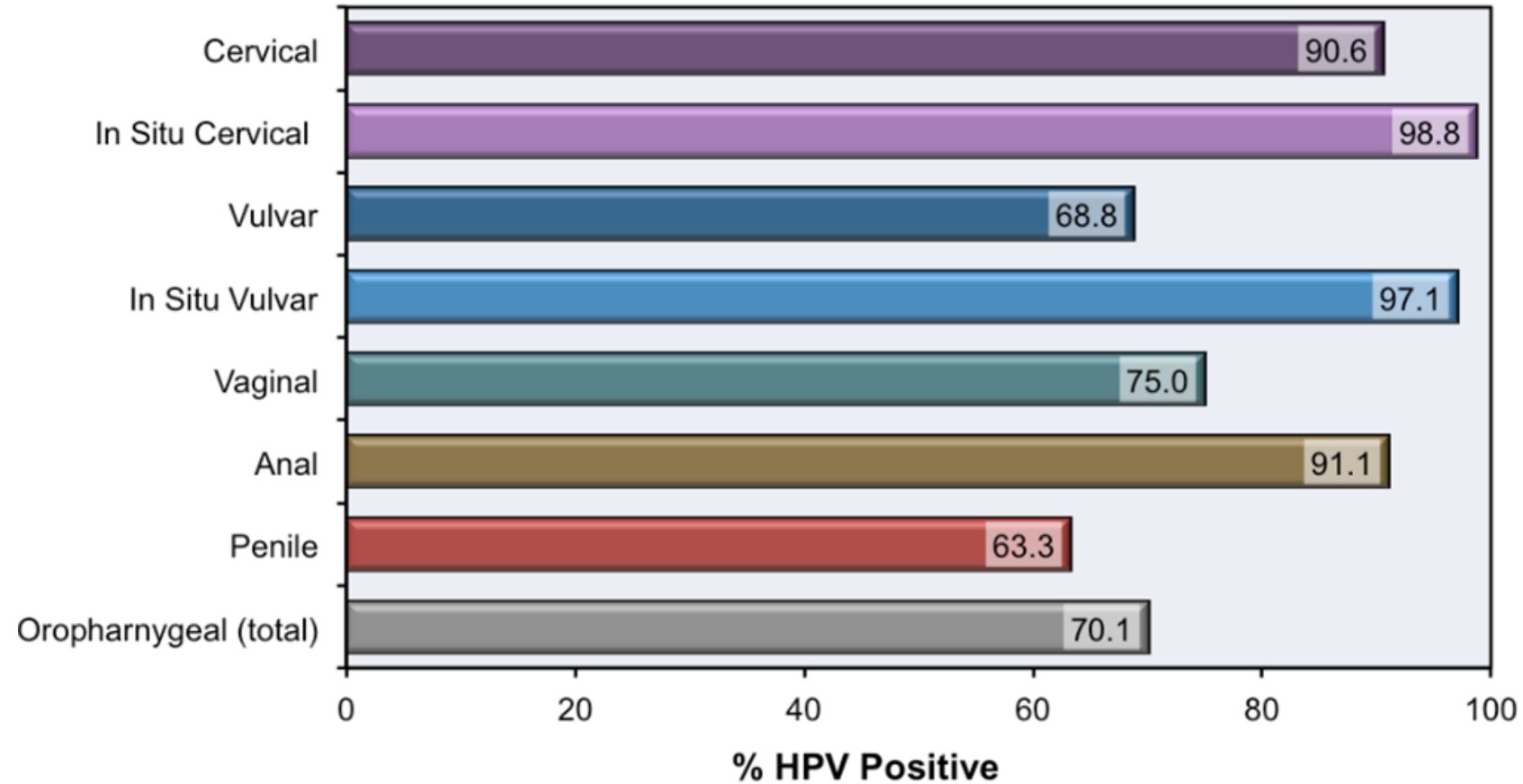


Abnormal cytology in MSM [HIV+ vs HIV negative]

Cancers caused by HPV

Cancers caused by HPV

- Many HPV infections are asymptomatic without clinical disease



*HPV types detected in genotyping study; most were high-risk HPV types known to cause cancer (Saraiya M et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. Journal of the National Cancer Institute 2015;107:djv086).

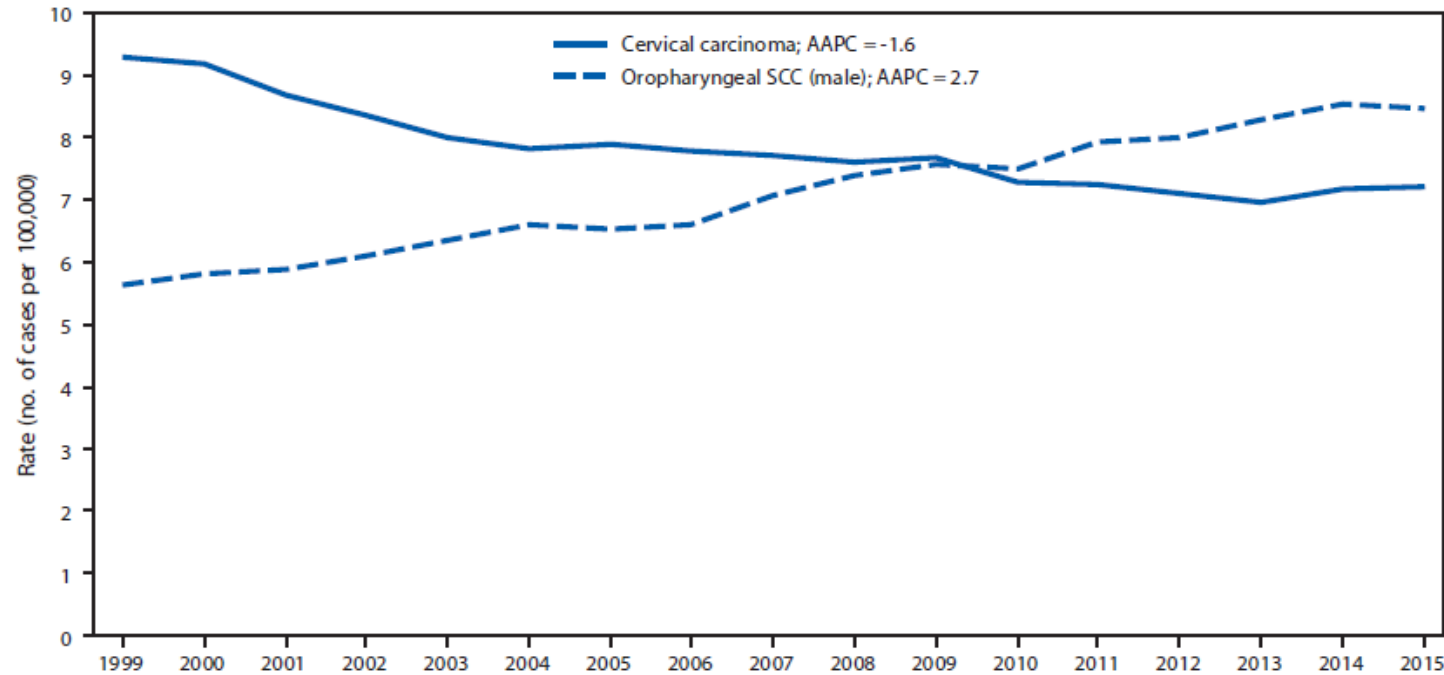
HIV + and Risk for HPV Associated Cancer

Cancer Type	Relative Risk [R5% CI]
Cervix	5.4 [3.9-7.2]
Vulva/Vagina	5.8 [3.0-10.2]
Penis	3.7 [2.0-6.2]
Anus (female)	6.8 [2.7-14.0]
Anus (male)	37.9 [33.0-43.4]
Tonsillar cancer (men)	2.6 [1.8-3.8]
Oropharynx	6.0 [3.5-9.7]

Oral Cancer

Trends in HPV Associated Cancers, US, 1999- 2015

FIGURE 1. Trends* in age-adjusted incidence of cervical carcinoma among females and oropharyngeal SCC among men,[†] — United States,[§] 1999–2015



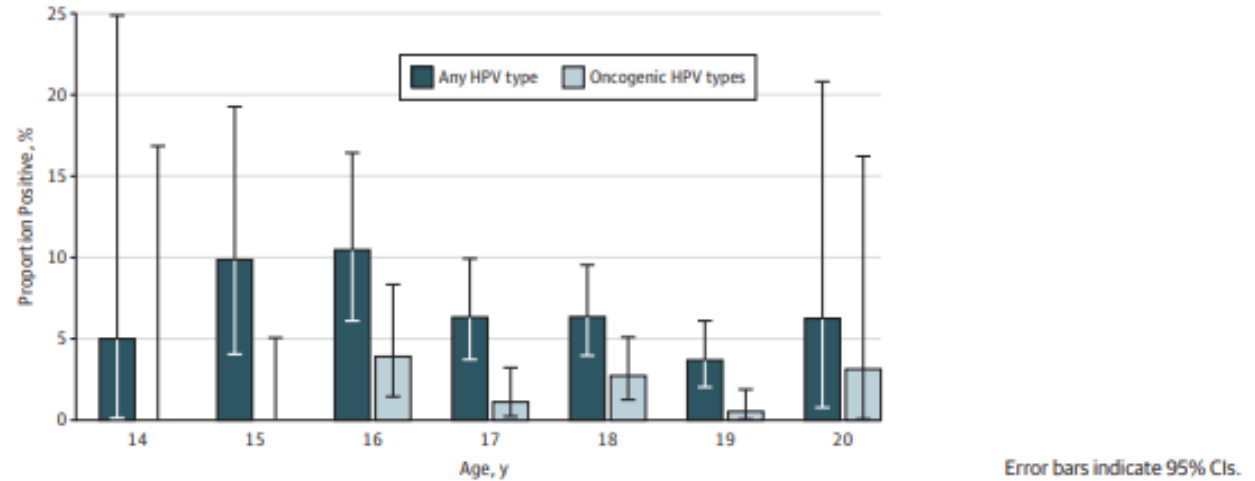
Oropharyngeal Cancer is the most common HPV associated cancer in Men
Cancer at back or throat, base of tongue and tonsils

USPTF recommendation: Screening for Oral Cancer

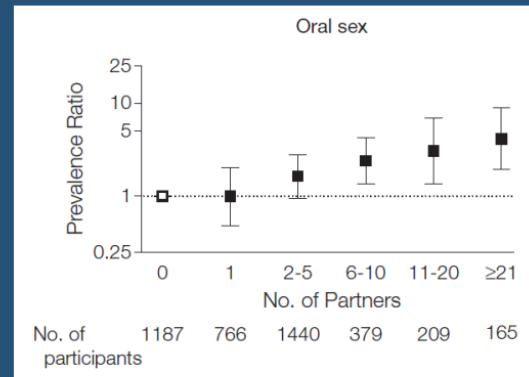
Population	Recommendation	Grade
Asymptomatic Adults	<p>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults.</p> <p>Go to the Clinical Considerations section for suggestions for practice regarding the I statement.</p> <p>Literature scans conducted in November 2020 in the MEDLINE, DARE, and PubMed databases and the Cochrane Library showed a lack of new evidence to support an updated systematic review on the topic at this time. See the Literature Surveillance Report under the Supporting Evidence section of this webpage.</p>	I

Oral Sex and HPV

- Two forms of oral cancer
 - Oral HPV infection
 - Cancer associated with smoking and alcohol use. HPV is one of the major causes of oral cancers in North America, Europe, and Japan
- HPV 16 has been a main cause of oral cancer
- Vaccination significantly decreases the vaccine subtypes in the oral cavity



Oral HPV Prevalence # lifetime ORAL sexual partners



# lifetime oral sex partners	Prevalence Ratio
0	– 3% prev
1	– 3%
2-5	– 6%
6-10	– 10%
11-20	– 15%
21+	– 22%

Gillison, Chaturvedi. JAMA 2012

What is the Risk Factor for Oral HPV Male vs Female “

	Men	Women
Any recent oral sex	3.15 (1.4-7.0)	0.66 (0.27-1.6)
# recent oral sex partners: 0	1.00	1.00
1	3.02 (1.3-6.8)	0.56 (0.22-1.4)
2	3.07 (1.1-8.9)	1.13 (0.39-3.2)
≥ 3	4.54 (1.4-14.8)	0.95 (0.19-4.8)
P-trend	0.001	0.86
Recent cunnilingus (oral sex on a woman)	2.52 (1.3-5.0)	0.77 (0.31-1.9)
Recent fellatio (oral sex on a man)	0.85 (0.29-2.5)	0.43 (0.17-1.1)

D'Souza et al. *J Infect Dis.* 2016 Feb

Males may be less likely to clear oral HPV

Cervical Cancer

Cervical Cancer Screening

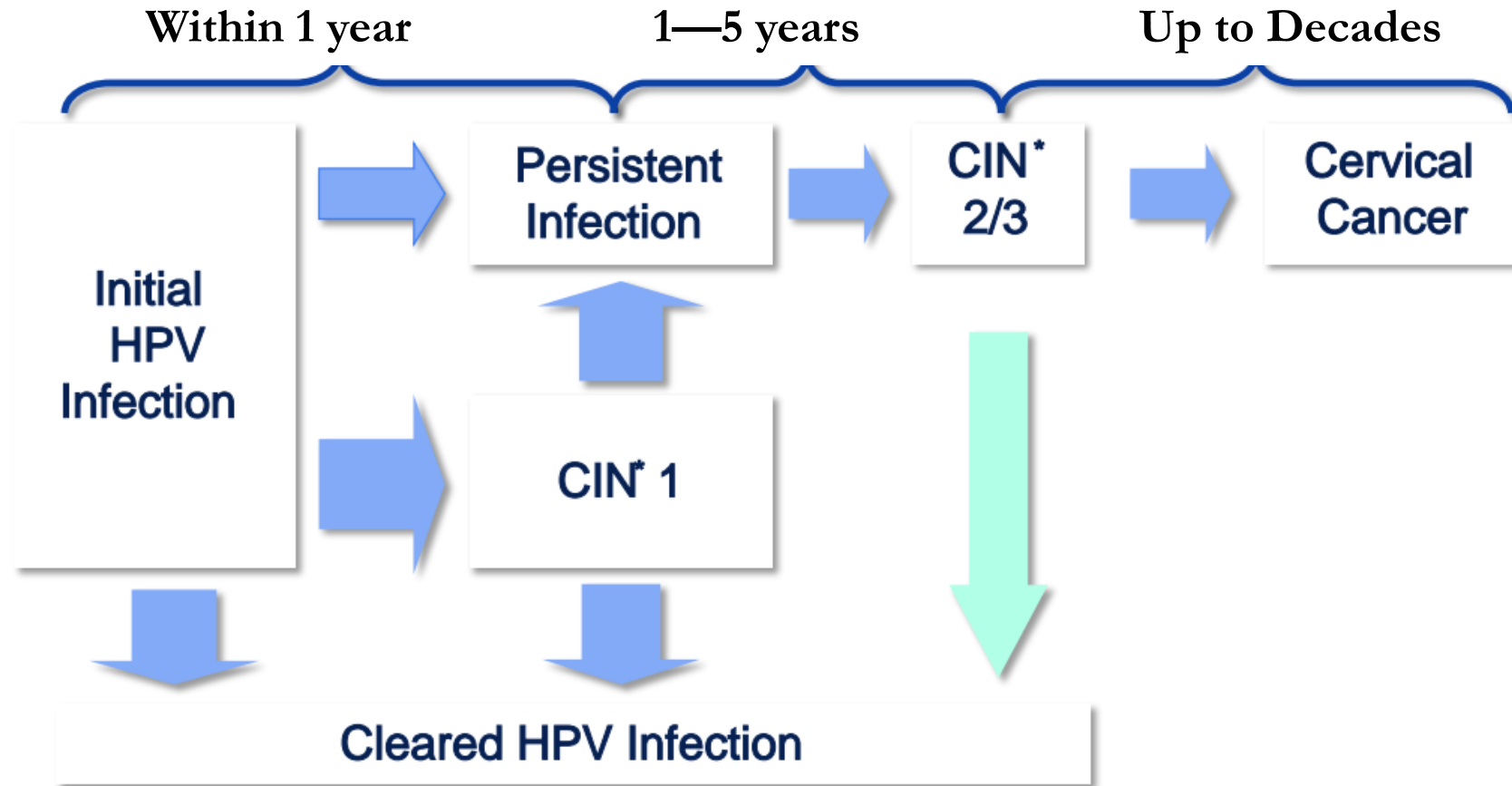
Cervical Cancer Screening Recommendations and Guidelines		
	ACS and ACOG, 2012	USPSTF, 2018
Screening Methods for Women Based on Age		
Ages 21-29 years	Pap every 3 years	Pap every 3 years
Ages 30-65 years	1) Co-testing (HPV and Pap) every 5 years (preferred) 2) Pap alone every 3 years	1) Co-testing every 5 years 2) Pap alone every 3 years 3) HPV alone every 5 years
Age to start	Age 21 years	Age 21 years
Screening among fully vaccinated	Same as for non-vaccinated	Same as for non-vaccinated

*All guidelines recommend that women who have been adequately screened can discontinue Pap at age 65.

ACS: American Cancer Society
 USPSTF: US Preventive Services Task Force
 ACOG: American College of Obstetricians and Gynecologists

Cervical cancer: ~12,000 cases diagnosed annually in the US, - >4,000 deaths—even with screening and treatment.

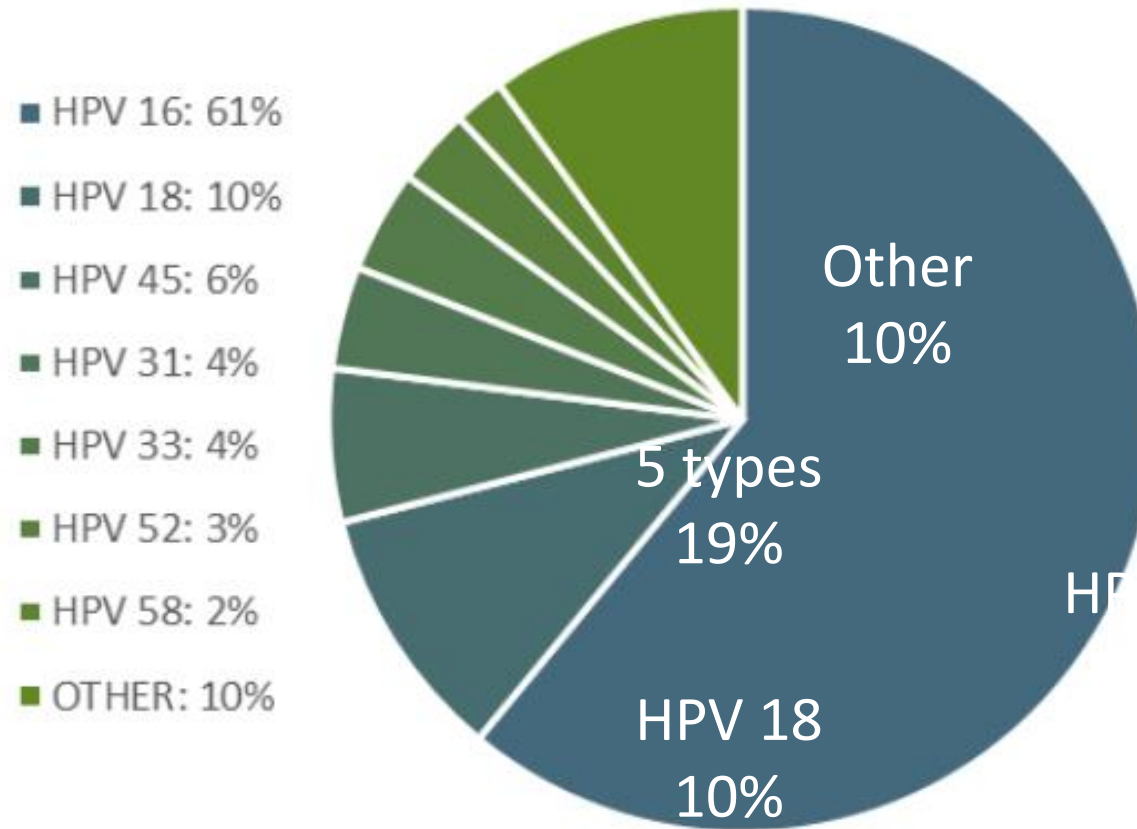
Natural History of HPV infection



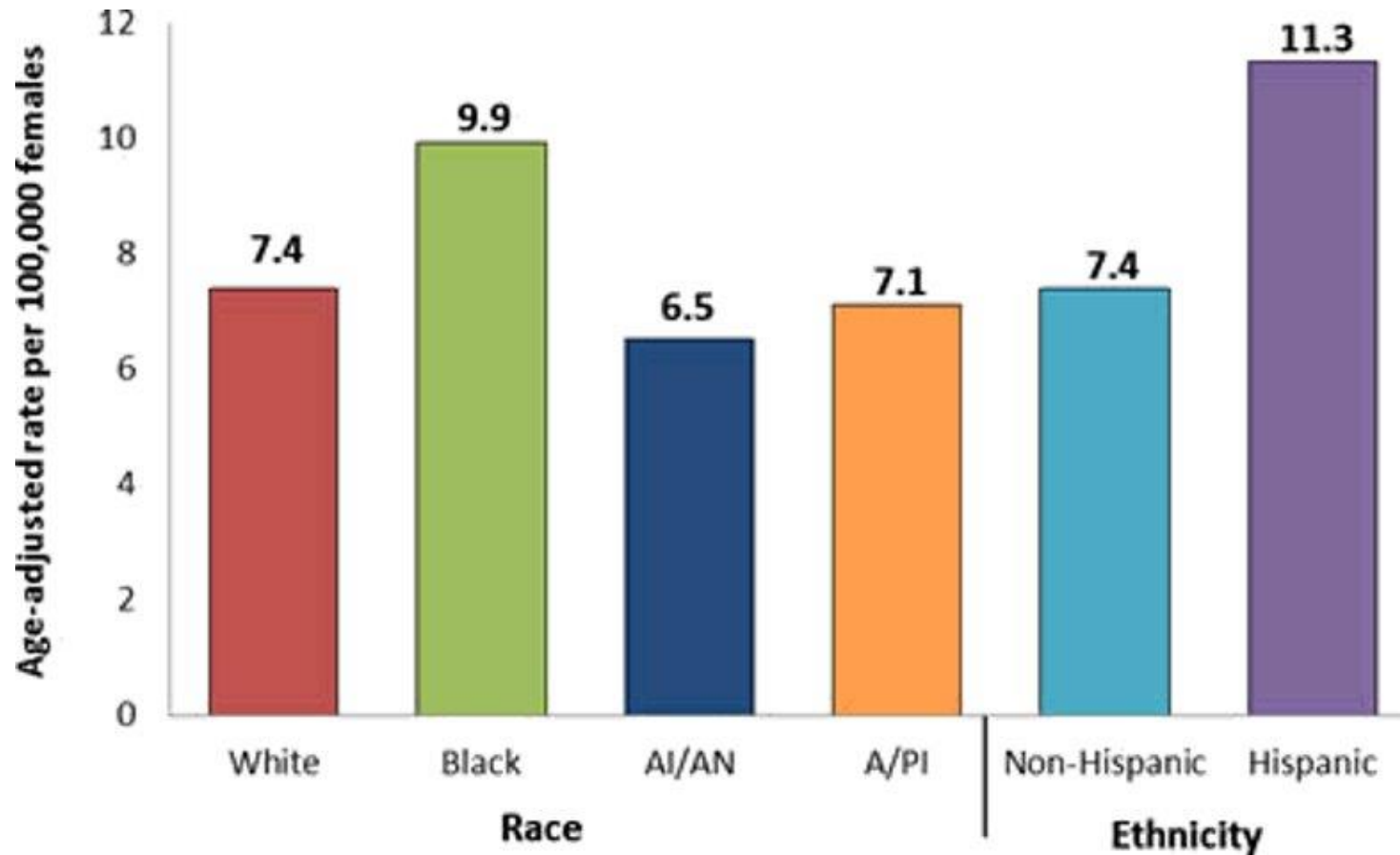
*CIN = cervical intraepithelial neoplasia

Discussion of tobacco use, and provision of cessation counseling, is important because of its contribution to the persistent infection and progression of HPV-related precancers and cancers



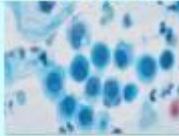
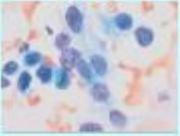


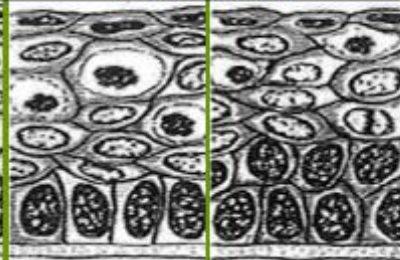
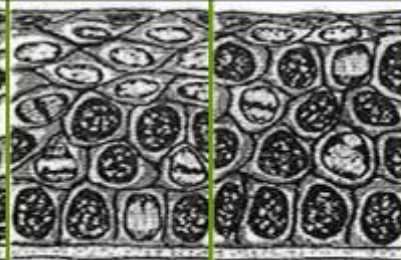


HPV types 16 & 18 cause most cases of cervical cancer



Disparities: HPV-Associated Cervical Cancer Rates by Race and Ethnicity, United States, 2004–2008



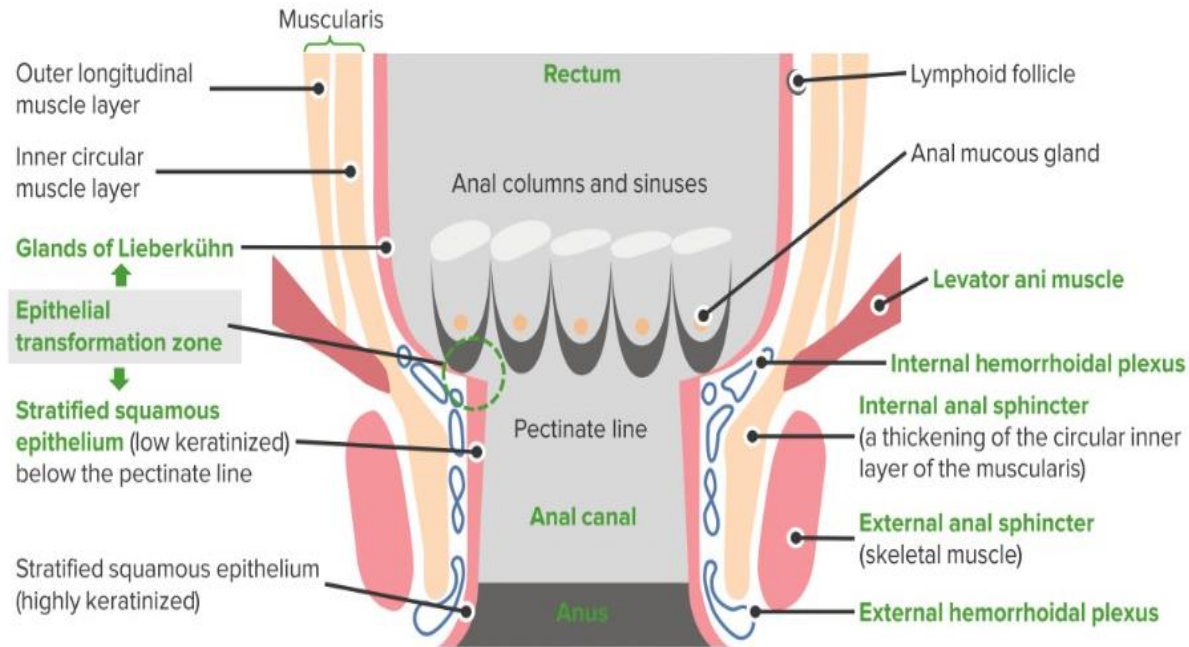
HPV Screening Terminology

	"low risk"		"high risk"		
General pathologic term	"low grade"		"high grade"		
Cytology	Normal 	ASCUS/LSIL 	HSIL 	CIS 	ICC 
Histology	Normal	(X)IN 1 (condyloma/mild dysplasia)	(X)IN 2 (moderate dysplasia)	(X)IN 3 (severe dysplasia/CIS)	Invasive Cancer
					

(X) can be cervical (C), anal (A), penile (P), vulvar (V), vaginal (VA)

Anal Cancer

Cervical and Anal Epithelium



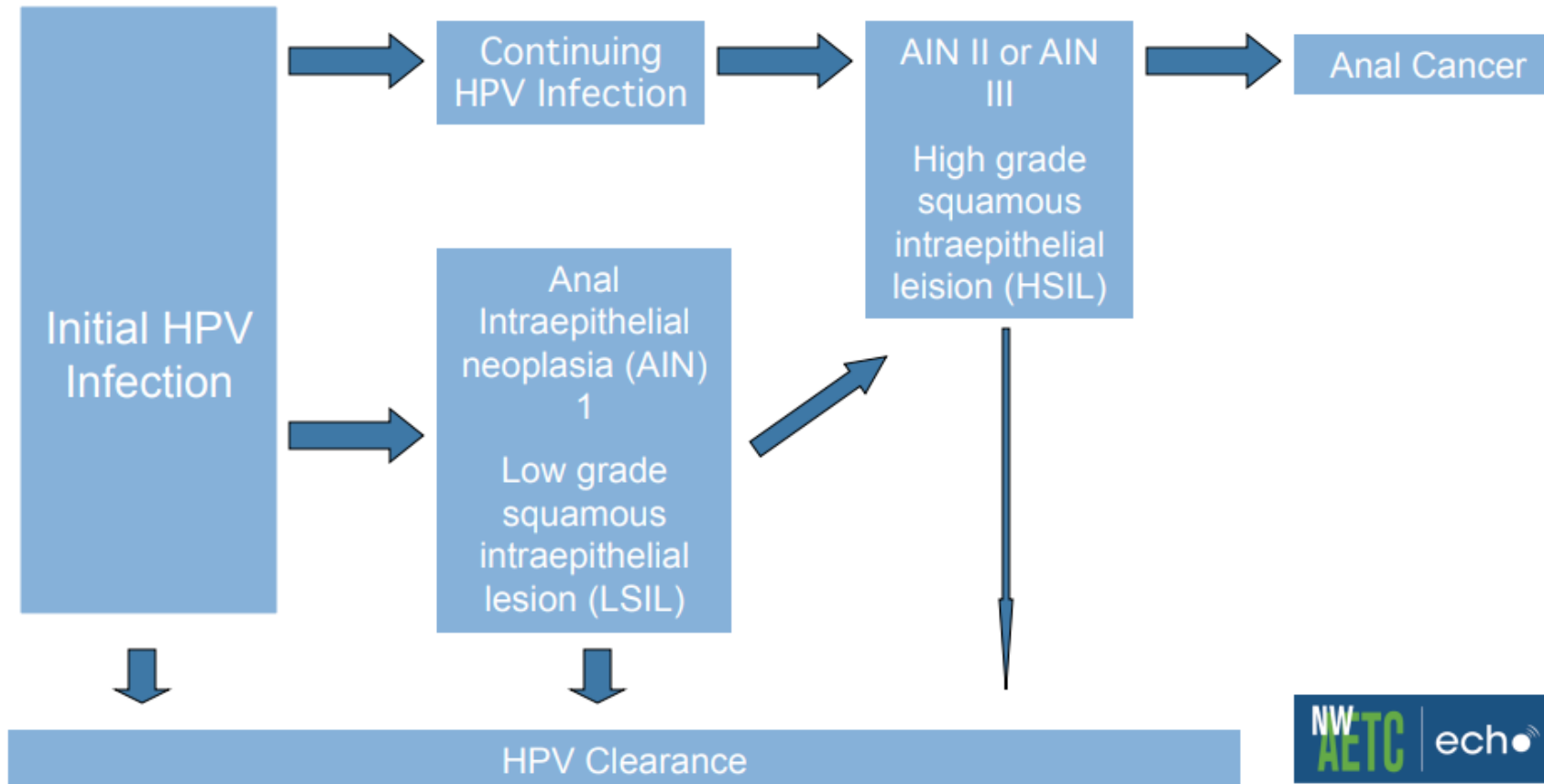
Anatomy of the anal canal

Image by Lecturio.

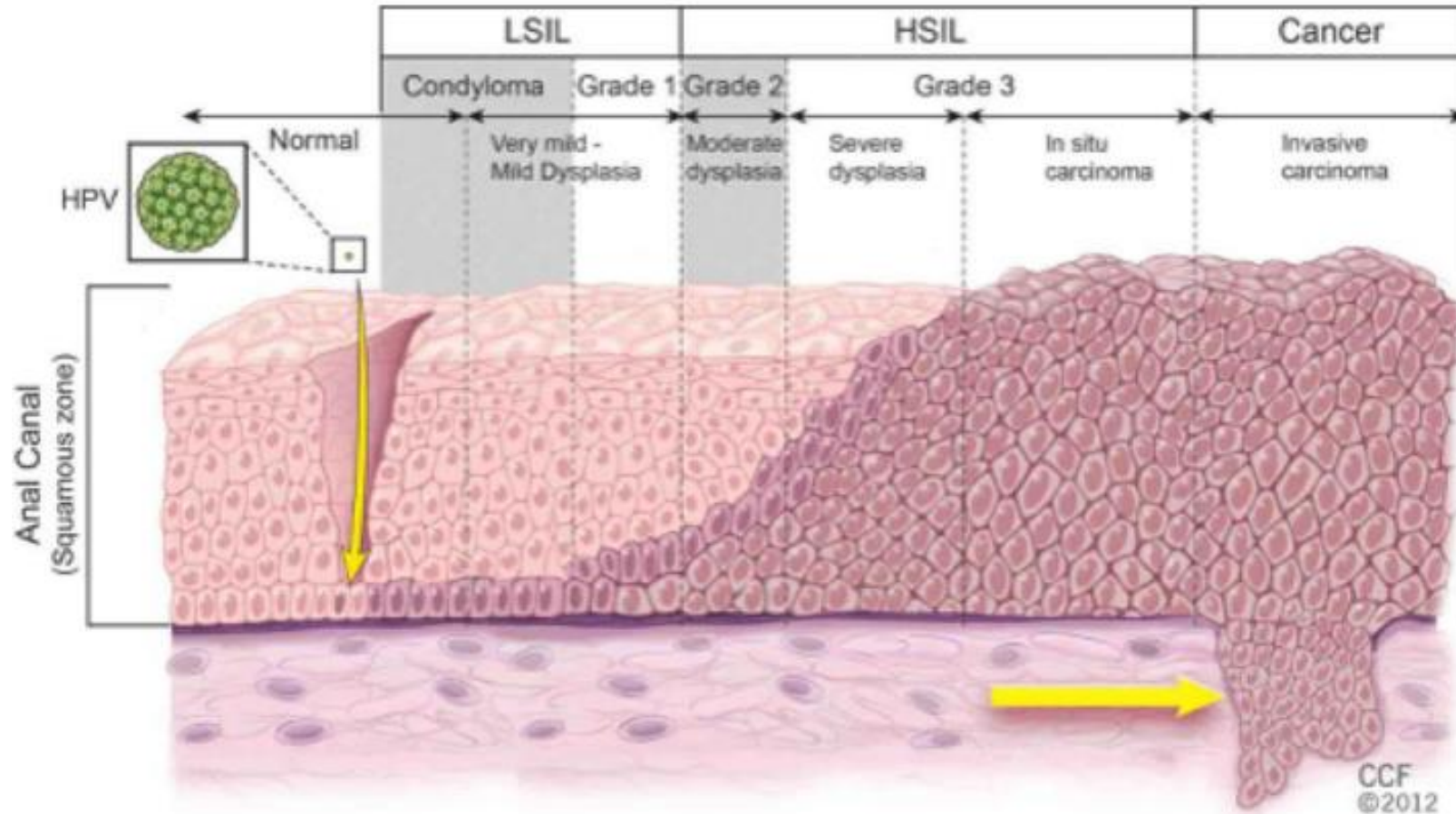
- Biological similarity between cervix & anus for area of HPV infection
- The transformation zone at the cervix has keratinized and squamous epithelium.
- The transformation zone at the dentate line of the anus between the squamous epithelium and the columnar epithelium of the rectum.

Anal Cancer Natural History

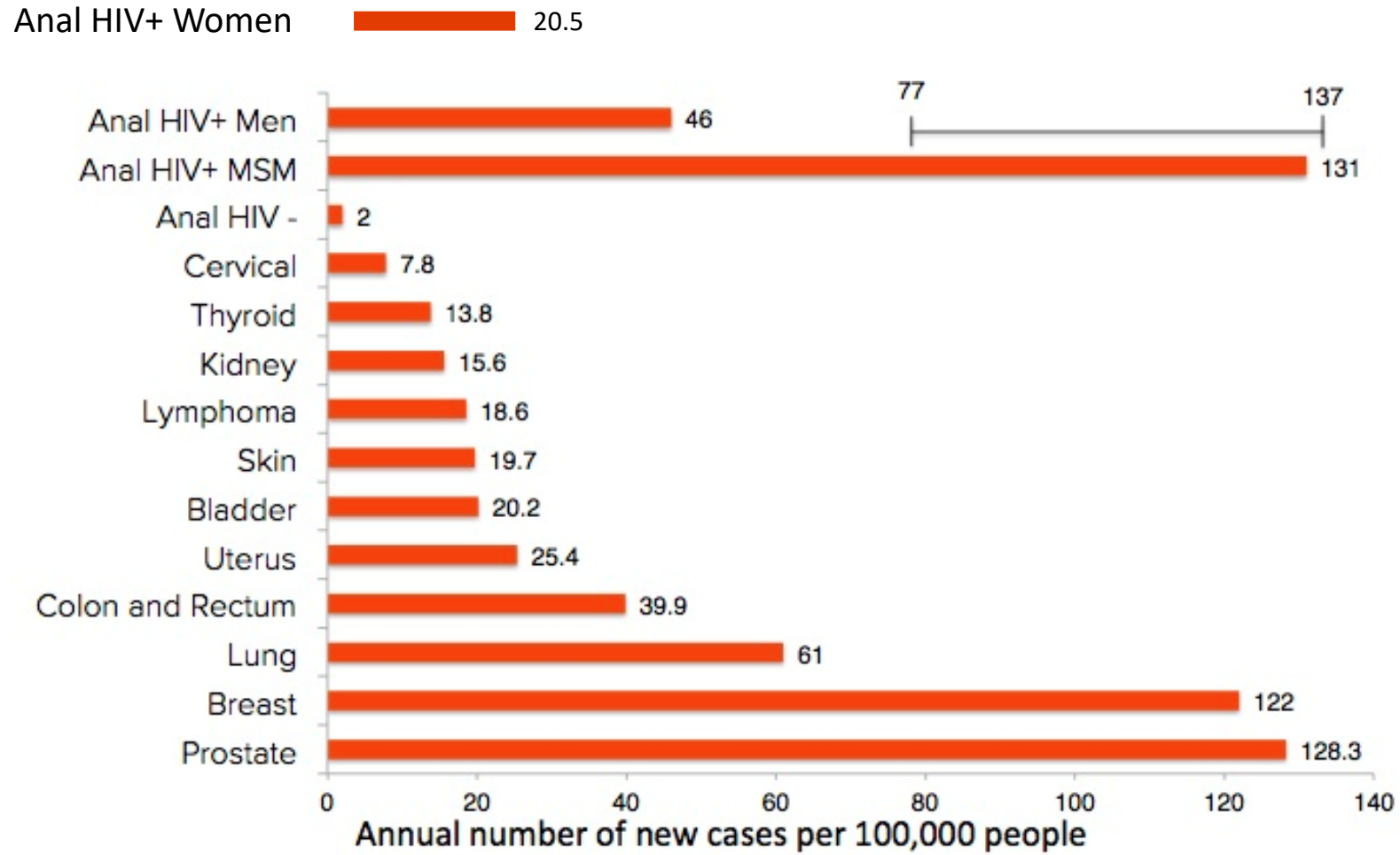
- Like cervical cancer, anal cancer is thought to progress from a precancerous lesions, anal intraepithelial neoplasia (AIN)



Anal Dysplasia



Anal Cancer Rates: Perspective



Type specific Anal HPV Prevalence, Among Men

Sexual Preference and HIV Infection Strong Independent Predictors of Male Anal HPV16

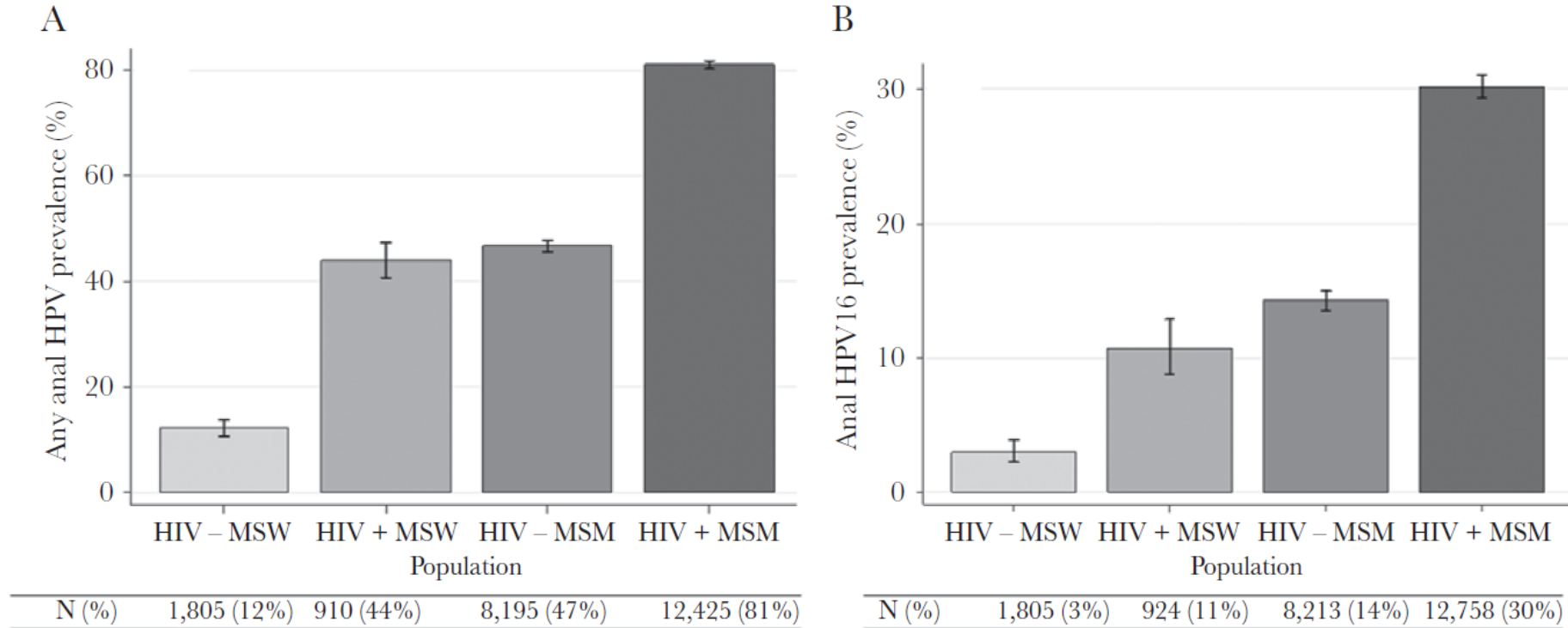


Figure 2. Prevalence of any anal human papillomavirus (HPV) infection (A) and anal HPV16 infection (B) by human immunodeficiency virus (HIV) status and sexual preference irrespective of anal diagnosis, including studies for which anal cytopathology diagnosis was unknown. Error bar: 95% CI. Abbreviations: MSM, men who have sex with men; MSW, men who have sex with women.

Who should be screened for Anal Cancer

People living with HIV

Men who have sex with men

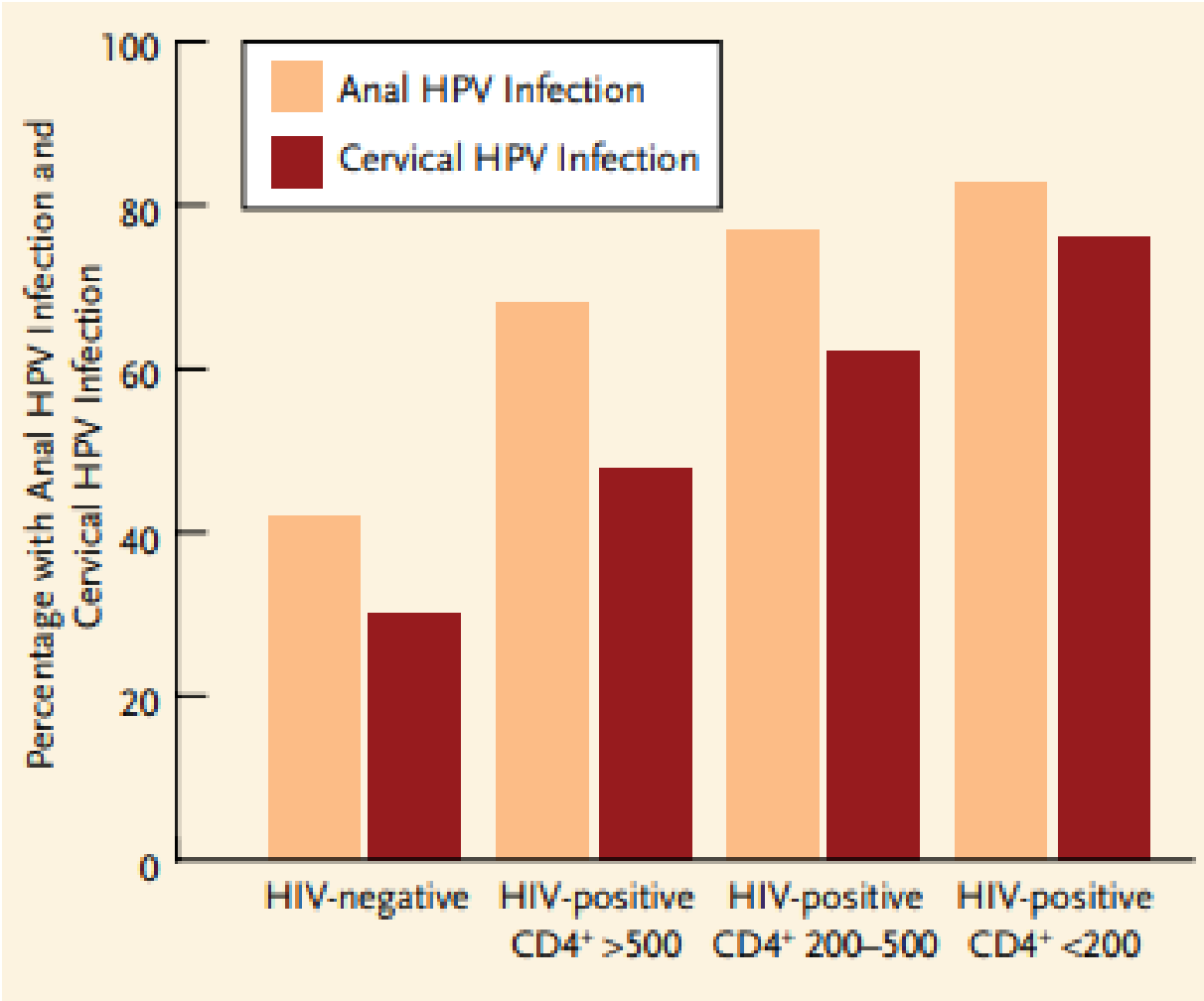
Iatrogenic immunosuppression (eg, solid organ transplant recipients, long-term oral corticosteroids)

Women with a history of cervical, vulvar, or vaginal SIL (also termed intraepithelial neoplasia) or cancer

Women with a history of cervical HPV 16 infection

Individuals with a history of anogenital warts

Anal & Cervical Cancer in HIV+ people by CD4 Count



Anal Cancer screening by Agency

<i>Agency</i>	<i>Year</i>	<i>Population</i>	<i>Age</i>	<i>Screening strategies/recommendations</i>	<i>Frequency</i>
<i>National and state-based guidelines</i> New York State Department of Health AIDS Institute²⁹	2007	<ul style="list-style-type: none"> ➤ All HIV-infected men and women ➤ Target high risk HIV-infected patients <ul style="list-style-type: none"> • MSM • History of anogenital condylomas • Women with history of cervical dysplasia 	All HIV-infected adults, regardless of age	<ul style="list-style-type: none"> ➤ Assessment as part of physical examination for all HIV patients <ul style="list-style-type: none"> • Inquire about any anal symptoms • Visual inspection of perianal area • DRE ➤ High risk patients should obtain anal Pap test <ul style="list-style-type: none"> • HRA with biopsy for all abnormal cytology 	Baseline and annual DRE and visual inspection for all HIV patients Annual anal Pap for high risk patients
Northwest Pennsylvania Rural AIDS Alliance¹⁹	2008	<ul style="list-style-type: none"> ➤ All HIV-infected men and women ➤ MSM are considered high risk 	No age specifications listed	<ul style="list-style-type: none"> ➤ Anal Pap included with initial evaluation after HIV diagnosis ➤ Annual Pap recommended for MSM ➤ HRA with biopsy for all abnormal cytology ➤ HRA also recommended for: <ul style="list-style-type: none"> • All patients at high risk for HPV or anal dysplasia, regardless of cytology • Prior history of cervical or anal HSILs • Visible or palpable anal lesions present 	Baseline anal Pap for all patients. Annual anal Pap for MSM with no expert agreement for women Patients with CD4 < 500 cells/mm ³ should be screened every 6–9 months with anal Pap
CDC Mortality and Morbidity Weekly Report²⁷	2009	<ul style="list-style-type: none"> ➤ All HIV-infected men and women 	Adults and adolescents	<ul style="list-style-type: none"> ➤ Visual inspection with DRE ➤ If anal cytology performed, abnormal findings should be followed with HRA with or without biopsy <ul style="list-style-type: none"> • Biopsy recommended only if diagnosis is uncertain 	Annual DRE and visual inspection

- ❑ All MSM, regardless of HIV status
 - HIV+: annually
 - HIV-: every 2-3 years
- ❑ Women with high-grade cervical or vulvar disease
- ❑ HIV-positive men and women, regardless of route of transmission
- ❑ Transplant recipients (immunocompromised)

Anal pap smear

- No preparation needed and no Anal sex for 48 hrs
- Insert swab [non wood] into canal until resistance [anal verge to distal rectum]
- Spiral motion with pressure and withdraw slowly (10 applying pressure to the wall while removing swab)
- Liquid-based cytology [swirl for 2 to 3 mins]
- Discard swab
- Do digital rectal exam after for masses

Sensitivity 69 to 93% and Specificity 23 to 59%
Refer all abnormal cytology for HRA:
ASC-US, LSIL, ASC-H, HSIL

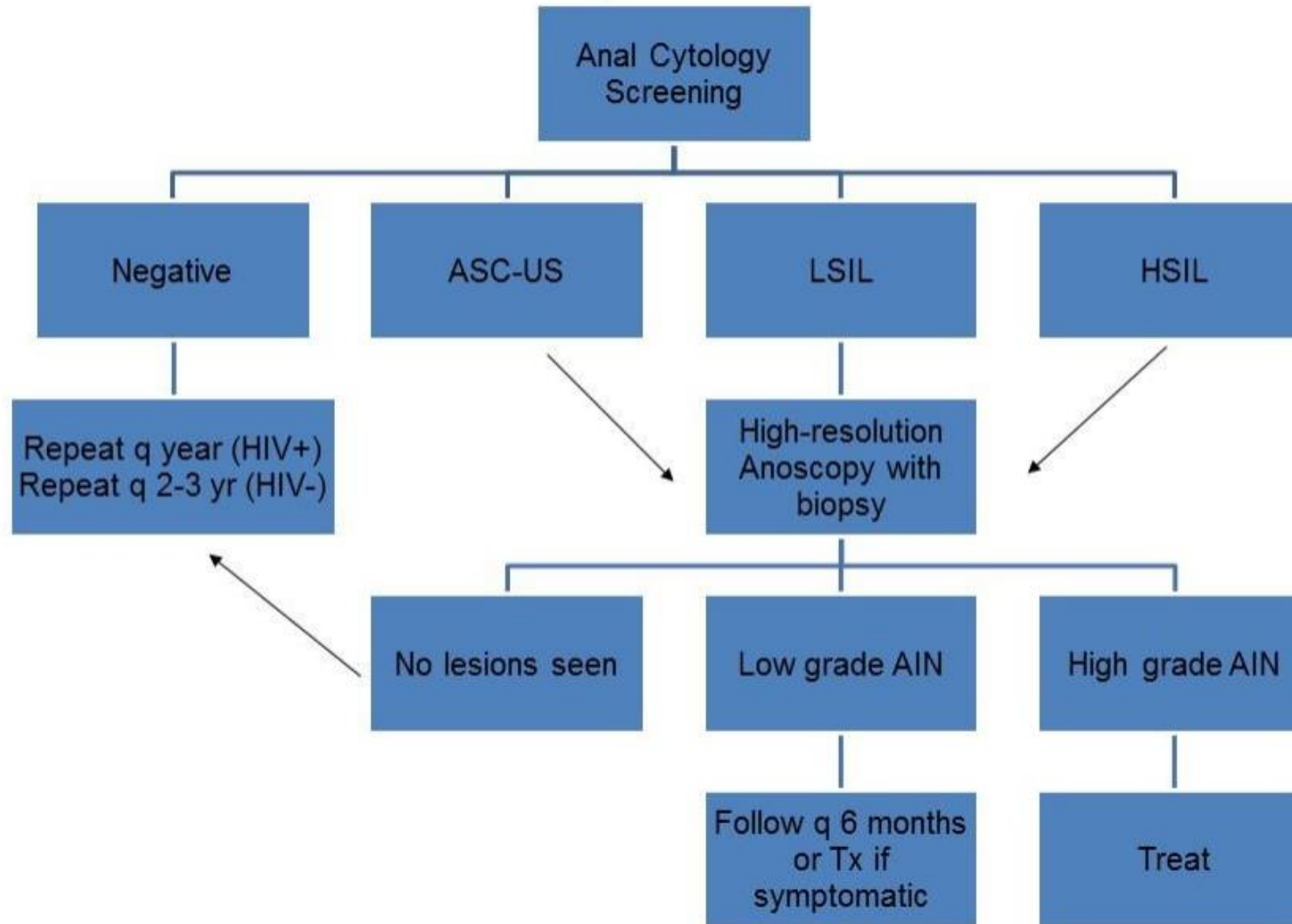
Chiao EY, Lensing SY. AIDS. 2020 Dec 1;34(15):2249-2258
Chiao EY, Giordona TP. Clin Infect Dis 2006;43(2):223-33

1. Wet dacron or rayon (NOT cotton) swab ~1½" into canal
 - No prior douching, enemas or K-Y
2. Gentle outward pressure swabbing circumference
3. Process using dry slide or liquid media



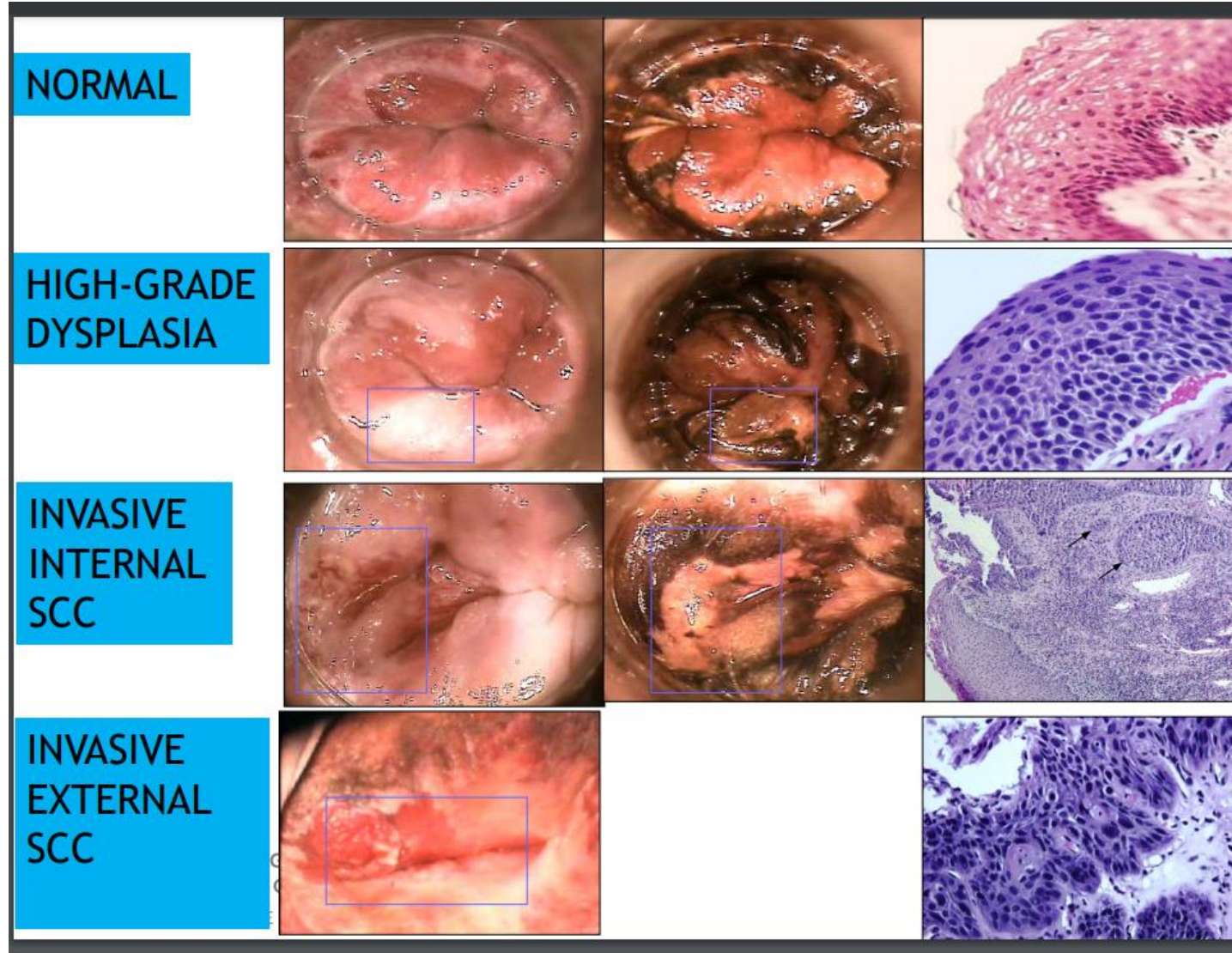
EM NATIONAL LGBT HEALTH
EDUCATION CENTER
A PROGRAM OF THE FENWAY INSTITUTE

Screening for Anal Cancer: Path report



High Resolution Anoscopy

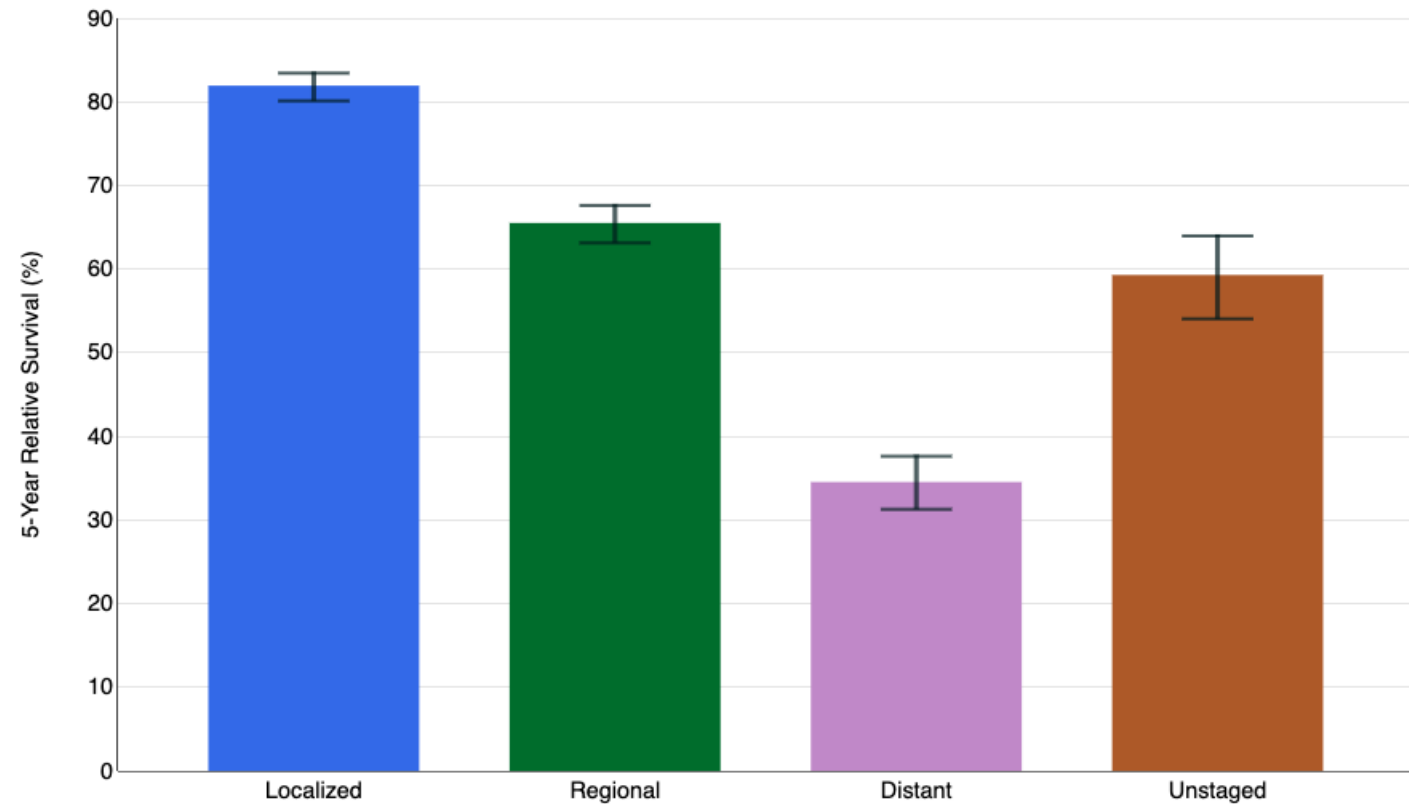




Digital Anorectal Exam (DARE)

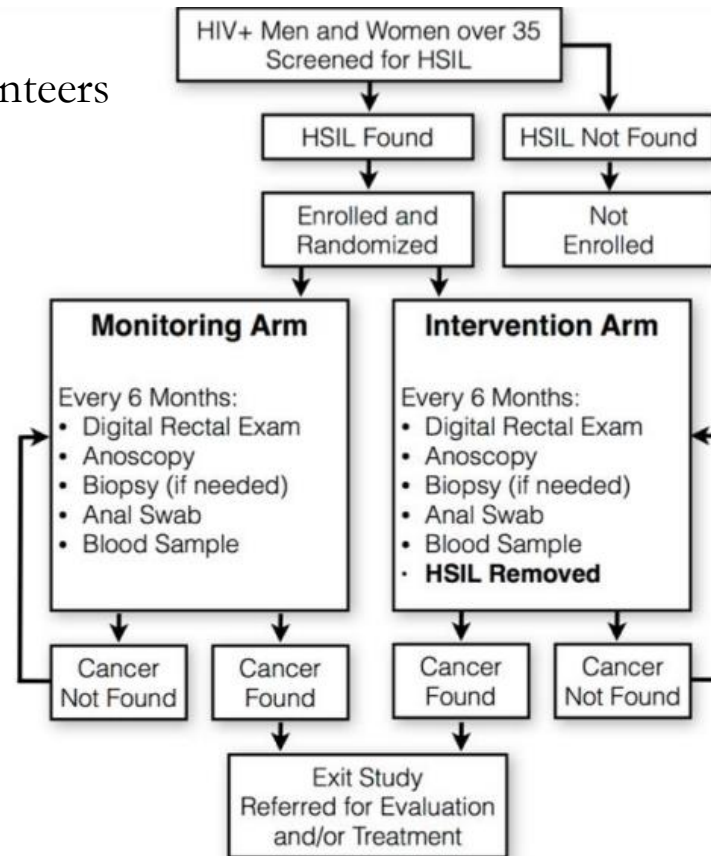
- Anal cancer survival related to stage
 - Superficially invasive cancer is treated
- Examine:
 - Circumference and length of anal canal and distal rectum
 - Anal margin: 5 cm distal to anal verge
 - Prostate
 - Pouch of Douglas

**Anus, Anal Canal & Anorectum
SEER 5-Year Relative Survival Rates, 2011-2017
By Stage at Diagnosis, Both Sexes, All Races (includes Hispanic), All Ages**



Anal Cancer/HSIL Outcomes Research (ANCHOR) The Anchor Study

Screened > 17,385
Enrolled 5058 study volunteers
Retained for 5 years



CLINICAL TRIALS & TRIBULATIONS

ANCHOR trial shows that treatment of anal high-grade squamous intraepithelial lesions prevents anal cancer in people with HIV

June 17, 2022 | Vol.48 No.24 | f t in e b

Before the results of the ANal Cancer/HSIL Outcomes Research (ANCHOR) study became available earlier this week, there was no clear reason to screen for the anal cancer precursor, anal high-grade squamous intraepithelial lesions (HSIL).

BYLINE

Joel M. Palefsky, MD
Professor of medicine and laboratory medicine, Head of AMC HPV Virology Core Lab, University of California San Francisco School of Medicine, Chair, HPV Working Group, AIDS Malignancy Consortium

Anal HSIL rarely causes symptoms, and essentially the only reason to treat it would be to prevent anal cancer, a benefit that had not yet been demonstrated. However, with the ANCHOR results, prevention of anal cancer by treating anal HSIL now provides a rationale to screen for and treat anal HSIL in people with HIV (PWH), and possibly others at increased risk of anal cancer.

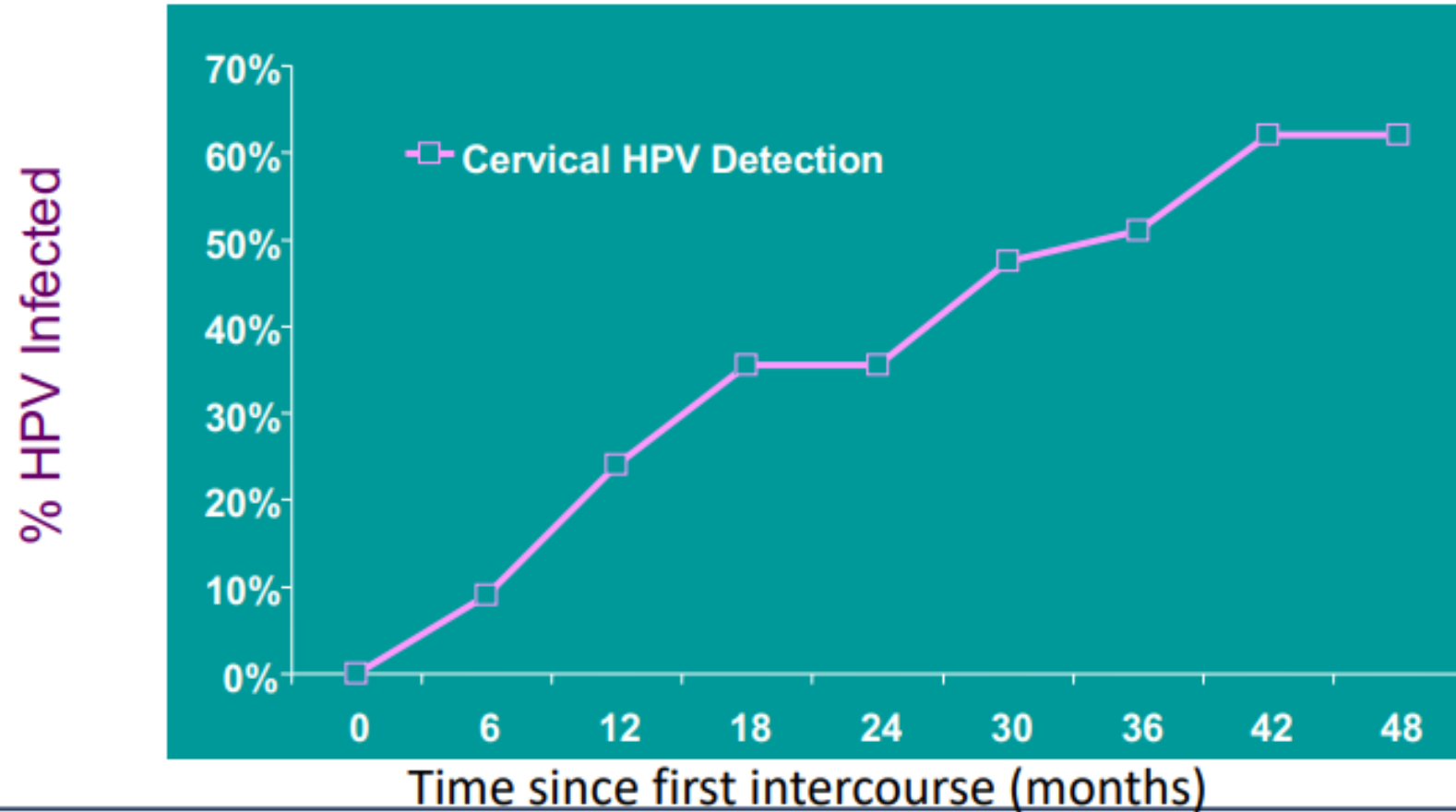
In People living with HIV treating anal precancerous -high-grade-HSIL, reduces the chance that anal cancer will develop by more than half

Patient FAQ's . How can I protect myself against HPV

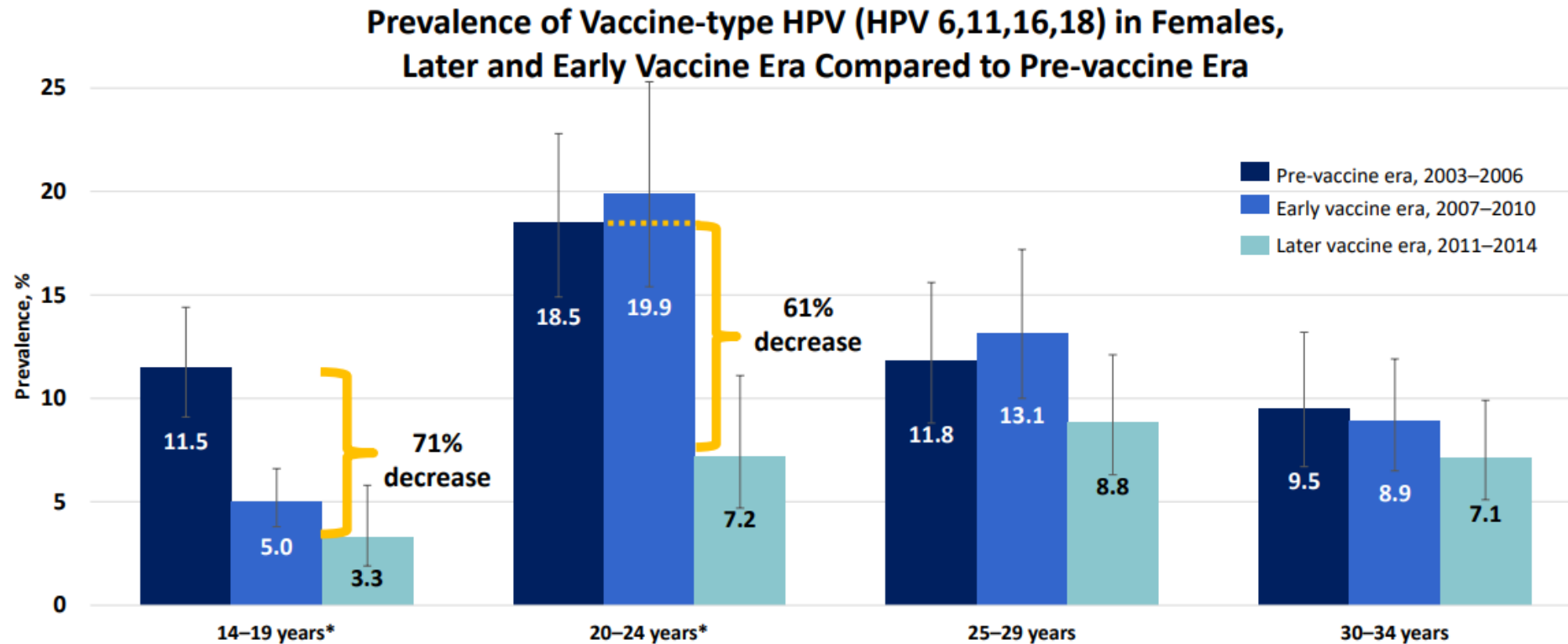
- Get vaccinated. The HPV vaccine is safe and effective. It can protect against diseases (including cancers) caused by HPV when given in the recommended age groups
- If you are sexually active use latex condoms the right way every time you have sex. This can lower your chances of getting HPV.
- HPV can infect areas not covered by a condom - so condoms may not fully protect against getting HPV

Prevention

HPV in unvaccinated sexually active people with cervix



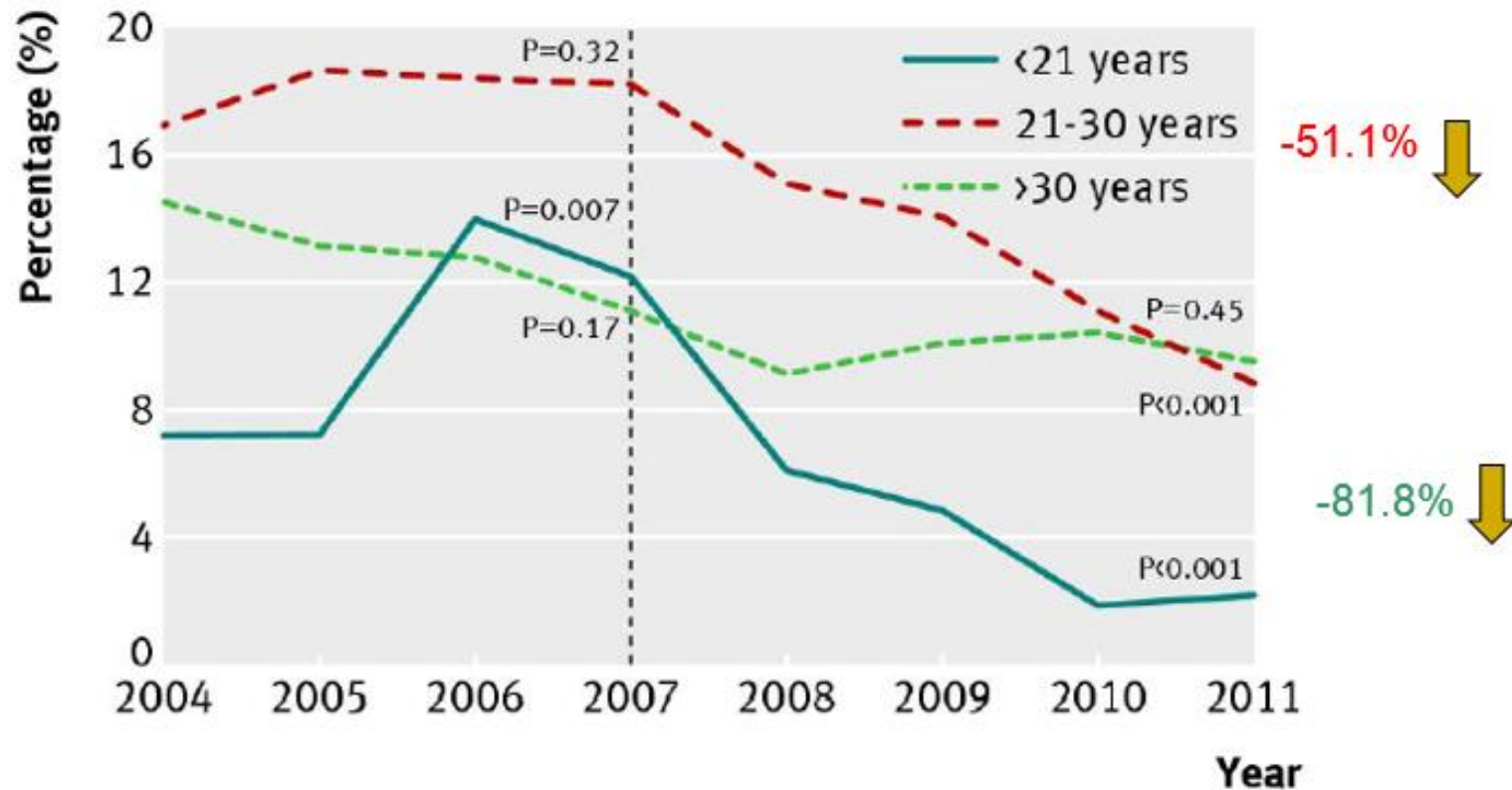
Cervical Precancer Incidence has decreased with Vaccine



Markowitz LE, Hariri S, Lin C, et al. *J Infect Dis* 2013 Aug 1;208(3):385-93
Oliver SE, Unger ER, Lewis R, et al. *J Infect Dis* 2017 Sep 1;216(5):594-603
NHANES: National Health and Nutrition Examination Survey

Vaccinating females leads to substantial herd protection from HPV in *heterosexual* males

Proportion of Australian-born heterosexual men attending sexual health clinics with genital warts by age group, 2004-2011



HPV Vaccine

Nanovalent HPV Vaccine

- Types 6, 11, 16, 18, 31, 33, 45, 52, 58
- FDA approved to prevent warts, cervical, vulvar, vaginal and anal cancer
- 2 doses for males/females aged 9-14
- 3 doses for males/females aged 15-26
- Immunocompromised patients need 3 doses, regardless of age of initiation

Morbidity and Mortality Weekly Report (*MMWR*)

[CDC](#) > [MMWR](#)

Use of a 2-Dose Schedule for Human Papillomavirus Vaccination – Updated Recommendations of the Advisory Committee on Immunization Practices

Weekly / December 16, 2016 / 65(49):1405-1408

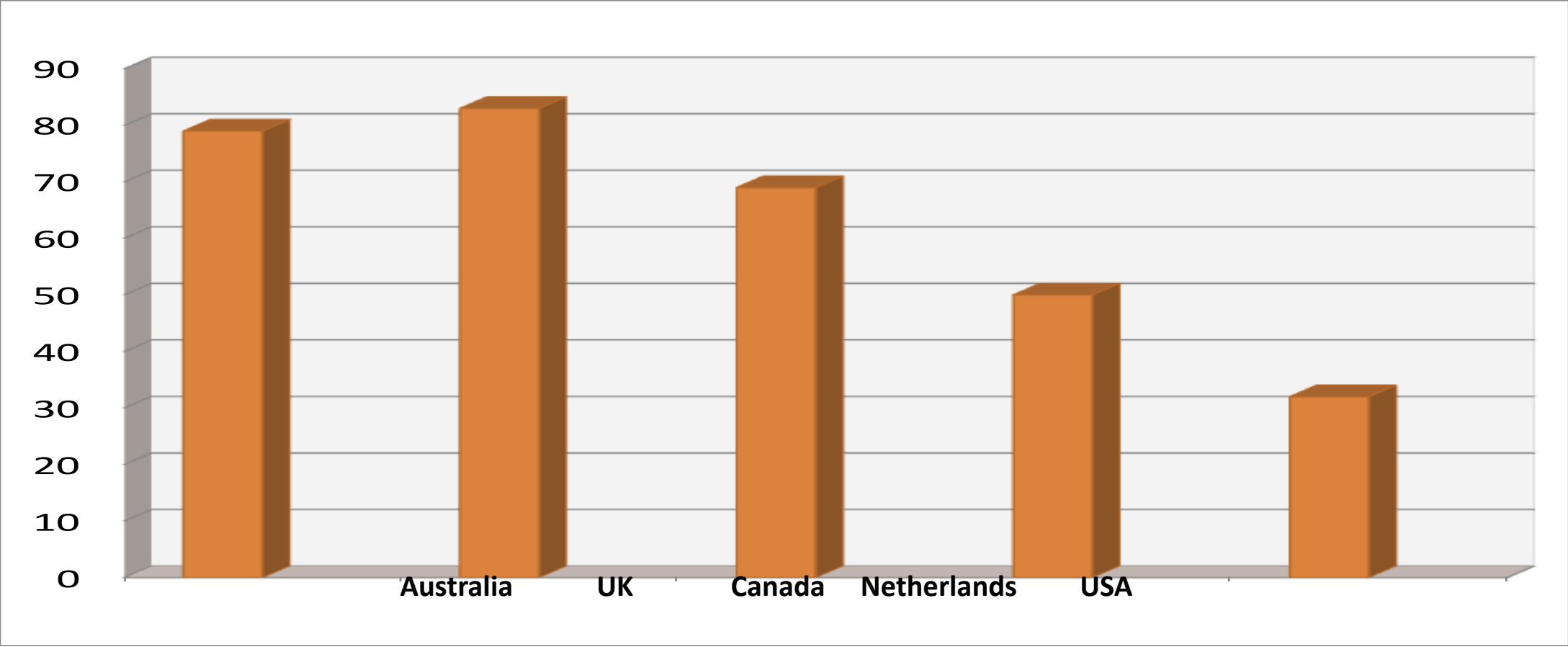
Recommended number of doses	Recommended dosing schedule	Population
2	0, 6–12 months*	Persons initiating vaccination at ages 9 through 14 years, except immunocompromised persons
3	0, 1–2, 6 months**	Persons initiating vaccination at ages 15 through 26 years, and immunocompromised persons initiating vaccination at ages 9 through 26 years; three-dose schedule also applies to adults initiating vaccination at ages 27 through 45 years.

Type of HPV Vaccine

HPV Vaccines	9-valent 9vHPV (Gardasil9)
L1 VLP types	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	Merck
Contraindications	Hypersensitivity to yeast
FDA Indications	Females (9-26 yrs): Anal, cervical, vaginal, and vulvar precancer and cancer; genital warts
	Males (9-26 yrs): Anal precancer and cancer; genital warts

1. High efficacy among females without evidence of infection with vaccine HPV types (>95%)
2. No evidence of efficacy against disease caused by vaccine types participants were infected with at the time of vaccination

International uptake doses HPV vaccine



Brotherton, Lancet 2011; Cuzick BJC 2010; Ogilvie et al., 2010; Marc et al., 2010, NIS-Teen 2011

HPV Vaccine for Persons 27 to 45

- Although new HPV infections are most commonly acquired in adolescence and young adulthood, some adults are at risk.
- At any age, a new sex partner is a risk for a new HPV infection.
- Most sexually active persons have been exposed to some HPV types, although not necessarily all of the types in the vaccine.
- HPV vaccines do not prevent progression of HPV infection, decrease time to HPV clearance, or treat HPV-related disease.

Effectiveness of HPV vaccine

HPV infections targeted by vaccine have decreased since vaccination was introduced*

Among teen girls†

88%



Among young women†

81%



HEALTH CARE PROVIDERS should recommend HPV vaccination for all patients at age 11 or 12[#]

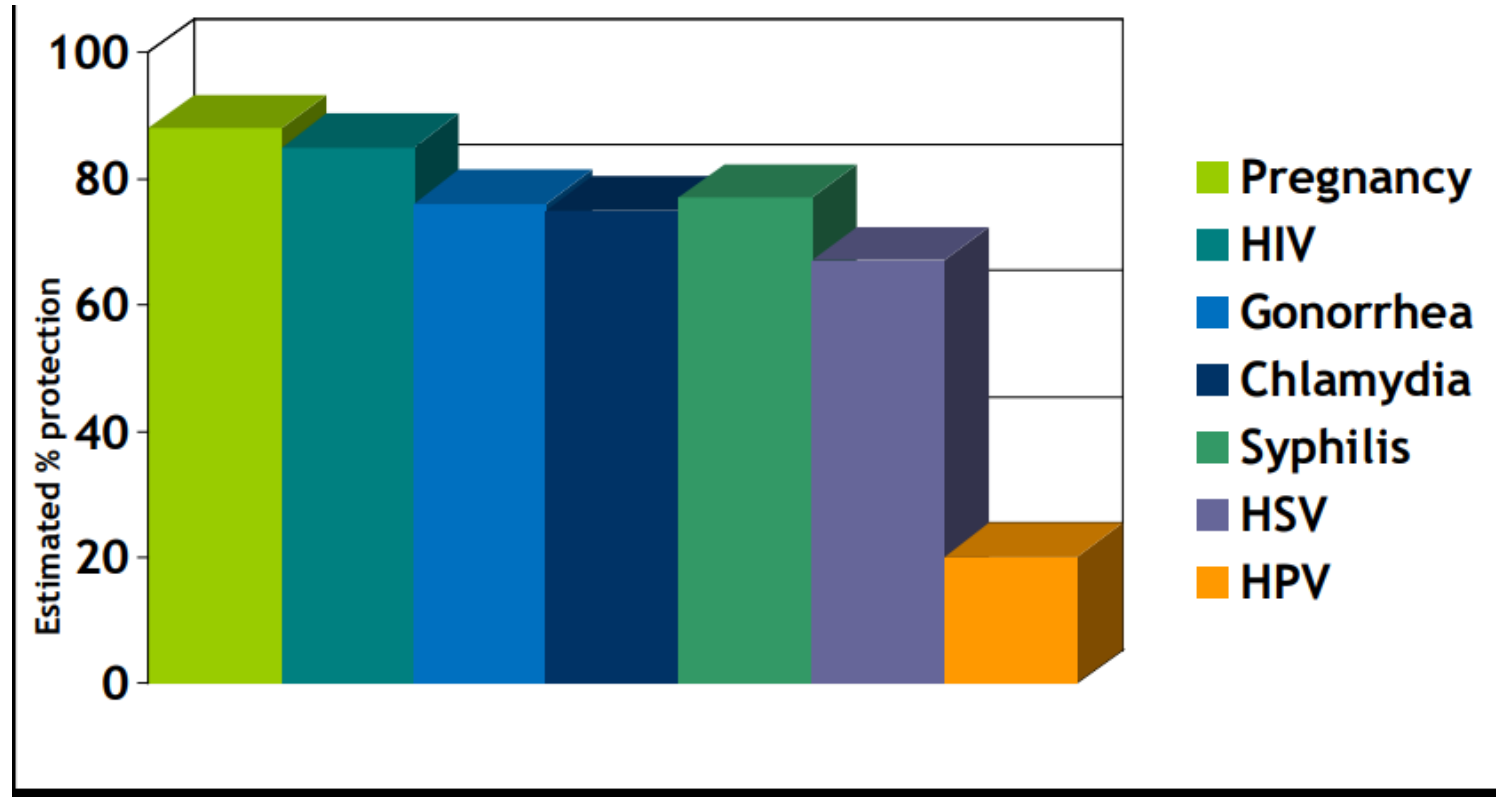
**HPV can cause some cancers in women and men
HPV vaccination is cancer prevention**

* HPV vaccination introduced in 2006

† Prevalence of HPV types targeted by the quadrivalent HPV vaccine among females aged 14-19 years and females aged 20-24 years in 2015-2018 compared with 2003-2006

[#] HPV vaccination is also recommended for everyone through age 26 years if not adequately vaccinated previously

Effectiveness of Condoms for HPV



Summary

- HPV causes a broad range of disease
- Some groups may have a higher risk for disease and need appropriate screening
- Acquisition of HPV related to early sexual activity
- HPV vaccines are safe and an effective way to prevent disease on a population
- Cervical cancer screening is important, in persons < 25 years have a low risk of persistence of infection
- Anal cancer screening is important for high-risk groups- however, there should be a referral pathway for follow up of abnormal results.