New developments in HIV-HPV co-infection

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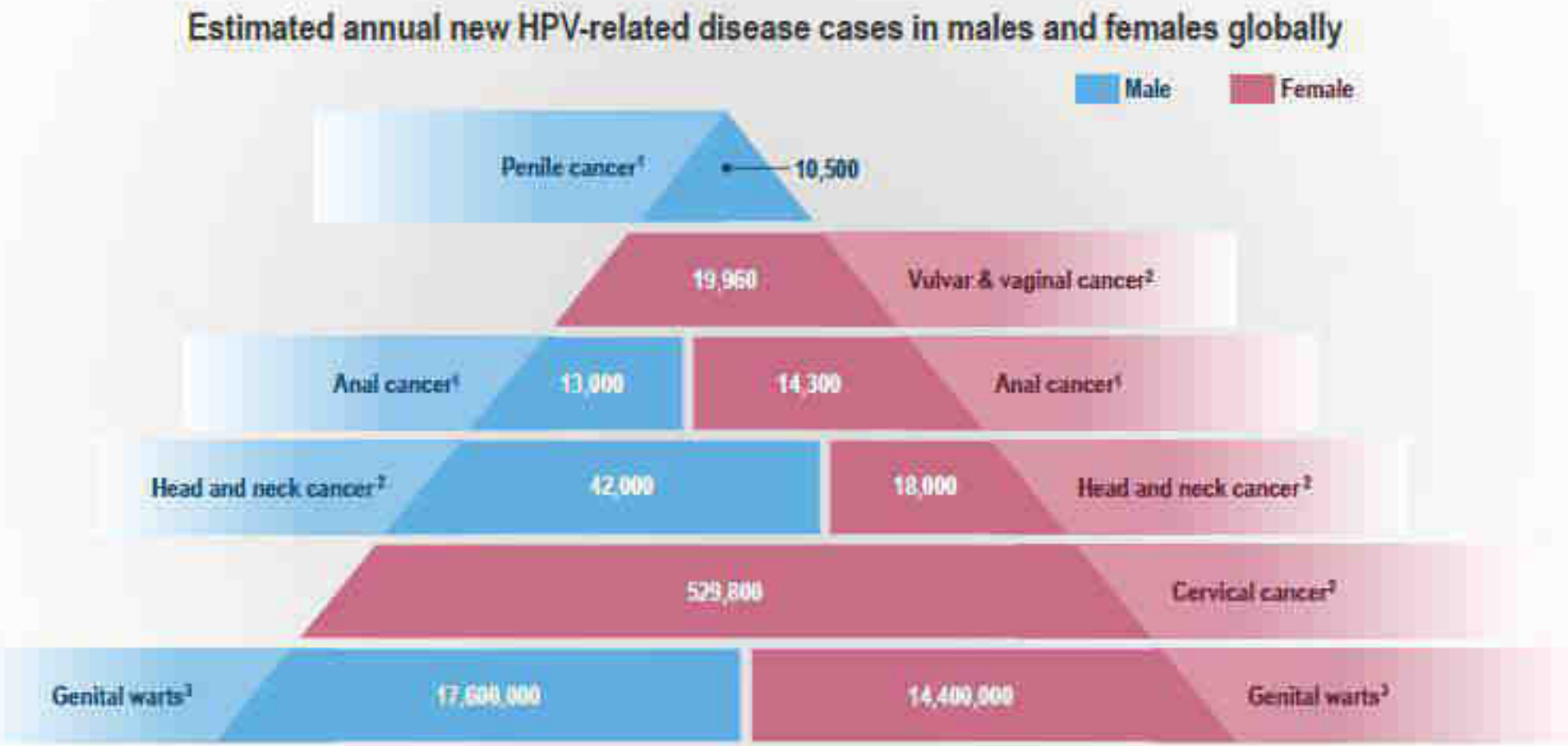
Outline

- Scope of the problem/trends in incidence
- What's new in primary prevention
- What's new in secondary prevention
- Emerging scientific questions

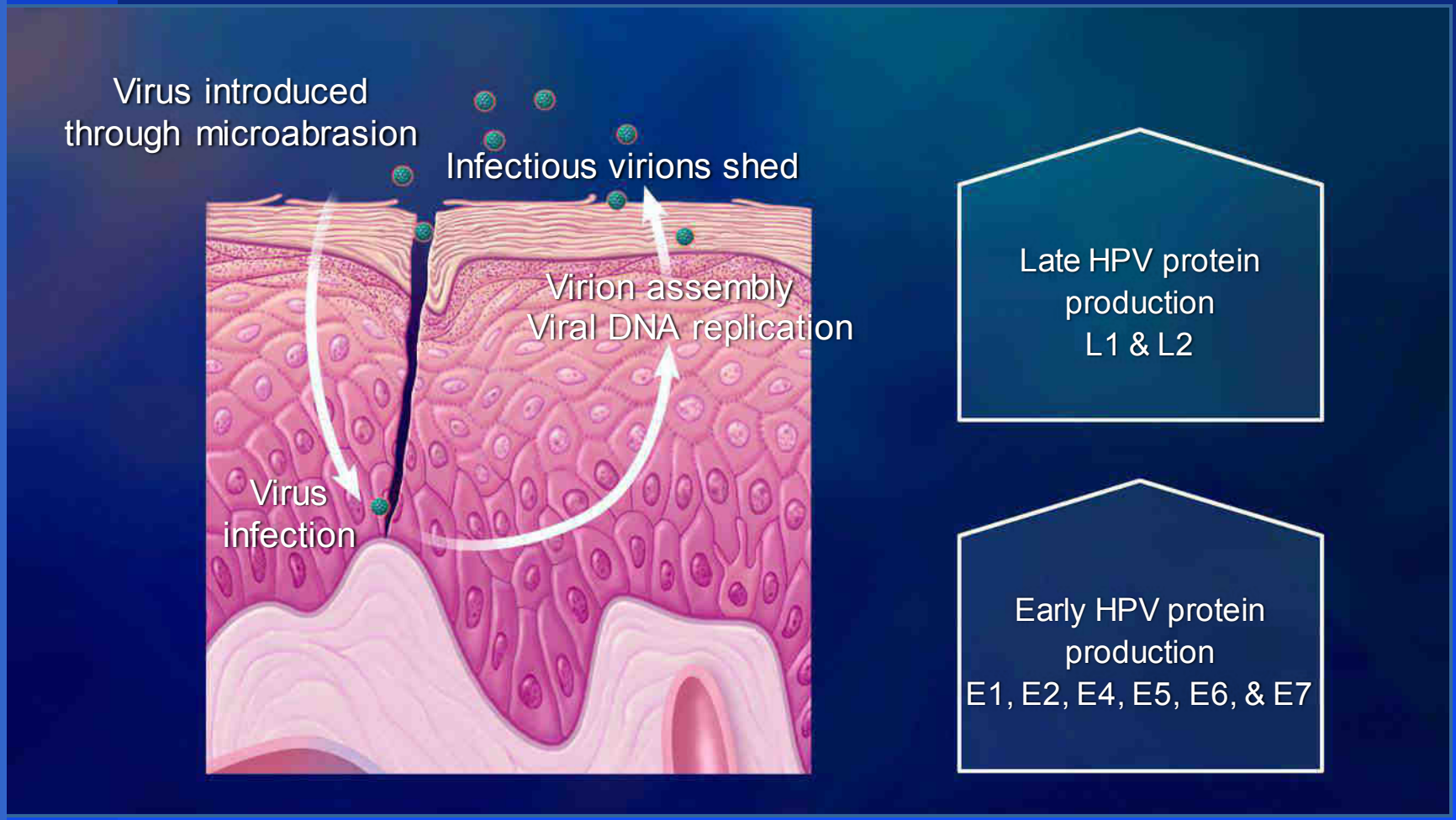
There Is a High HPV Disease Burden Among Males and Females Globally



Published HPV prevalence rates were applied as follows: Parkin D et al. *Vaccine*. 2006 (penile, vulvar, anal, cervical cancers); WHO/ICO 2010 (head and neck cancer); De Vuyst H et al. *Int J Cancer*. 2009 (vaginal cancer); Greer CE et al. *J Clin Microbiol*. 1995 (genital warts).

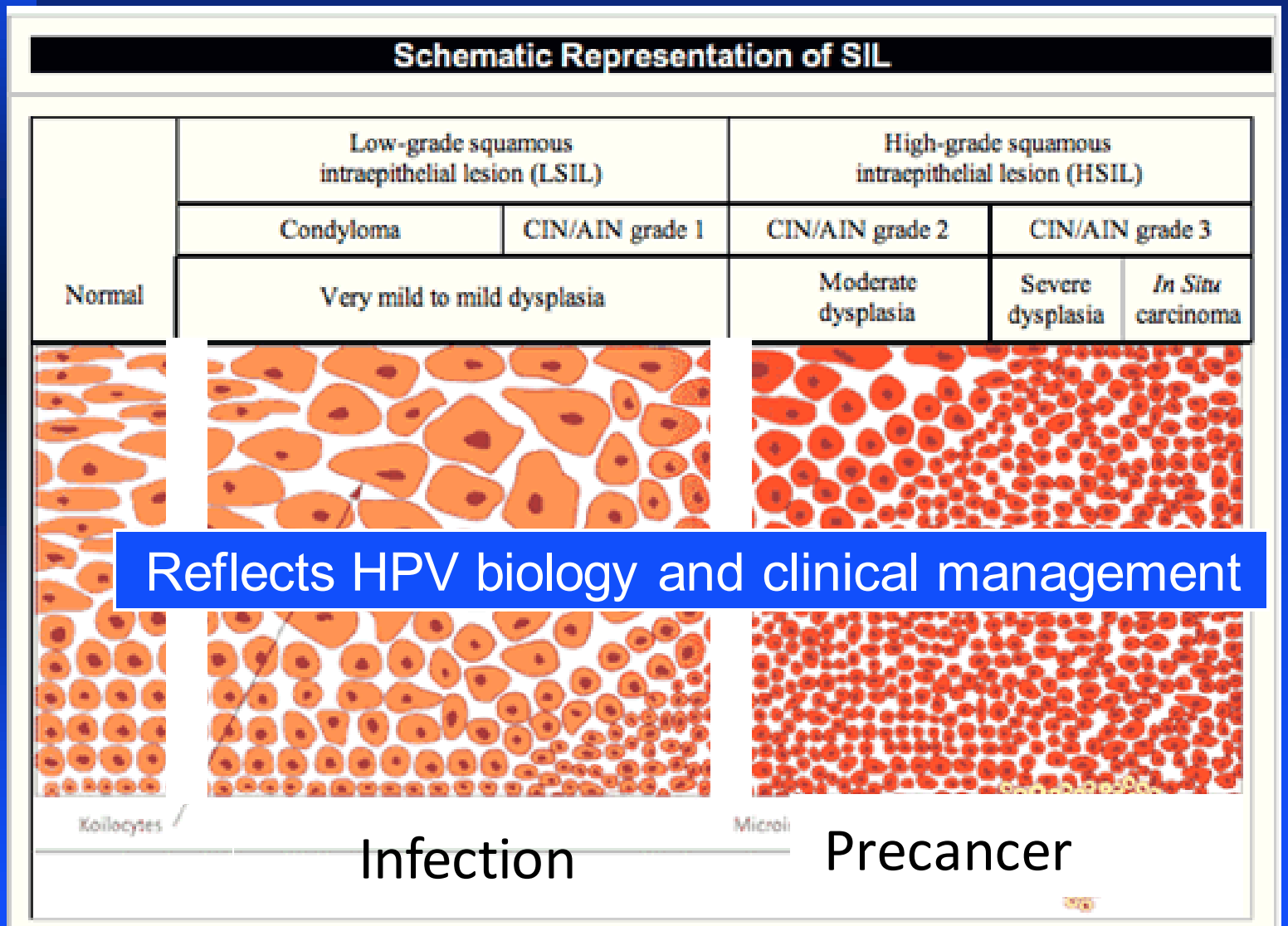
1. Parkin DM et al. *Vaccine*. 2006;24(Suppl 3):S3/11–S3/25. 2. WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Human Papillomavirus and Related Cancers in World. Summary Report 2010. http://www.who.int/hpvcentre/en/. Accessed June 21, 2012. 3. World Health Organization (WHO). Executive summary: the state of world health. 1995. http://www.who.int/whr/1995/media_centre/executive_summary1/en/index3.html#. Accessed June 7, 2012.

HPV Infection and Productive Life Cycle

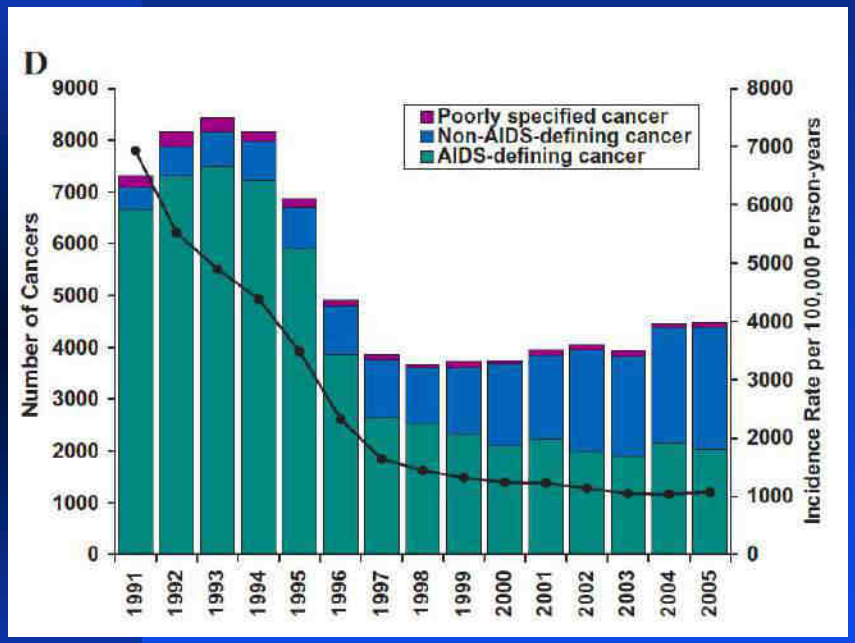


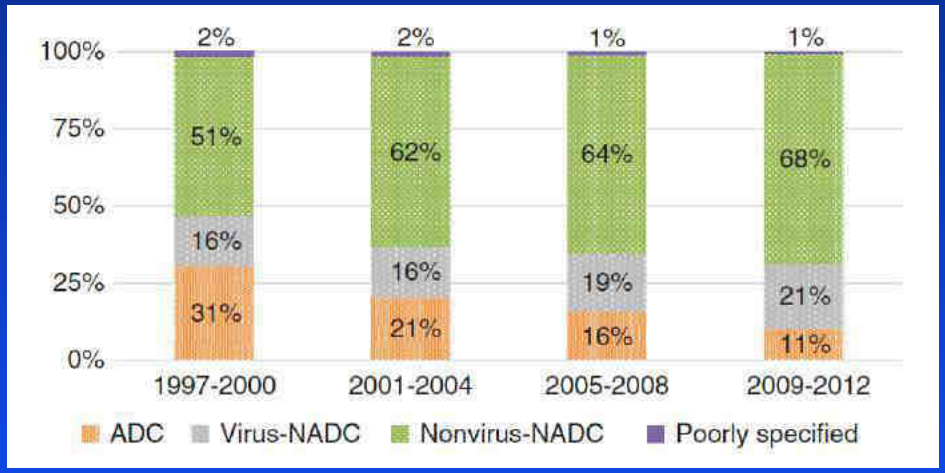
Adapted from Doorbar J. *J Clin Virol*. 2005;32S:S7–S15.

2-tiered system: LSIL & HSIL

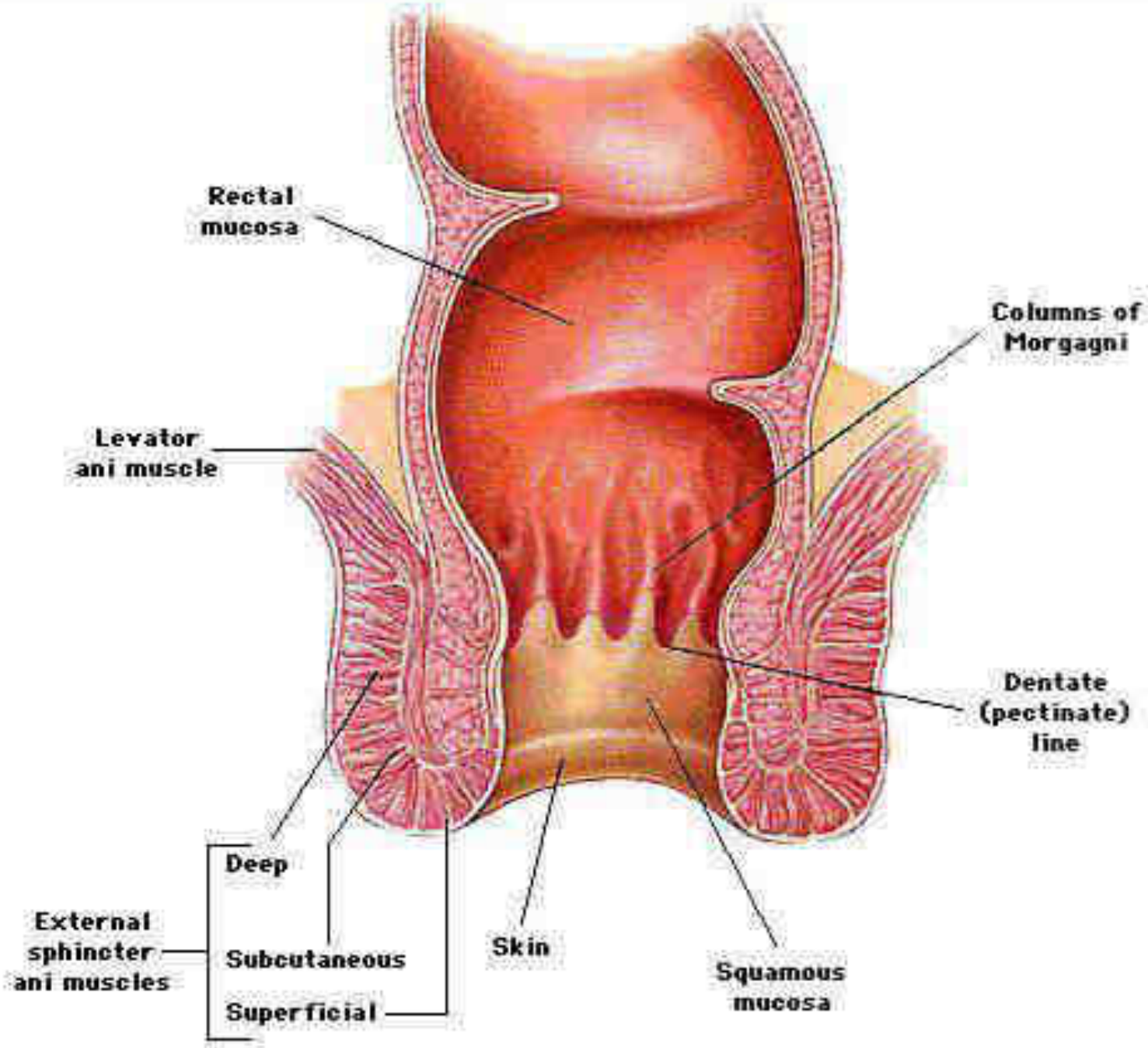


Distribution of cancers over time

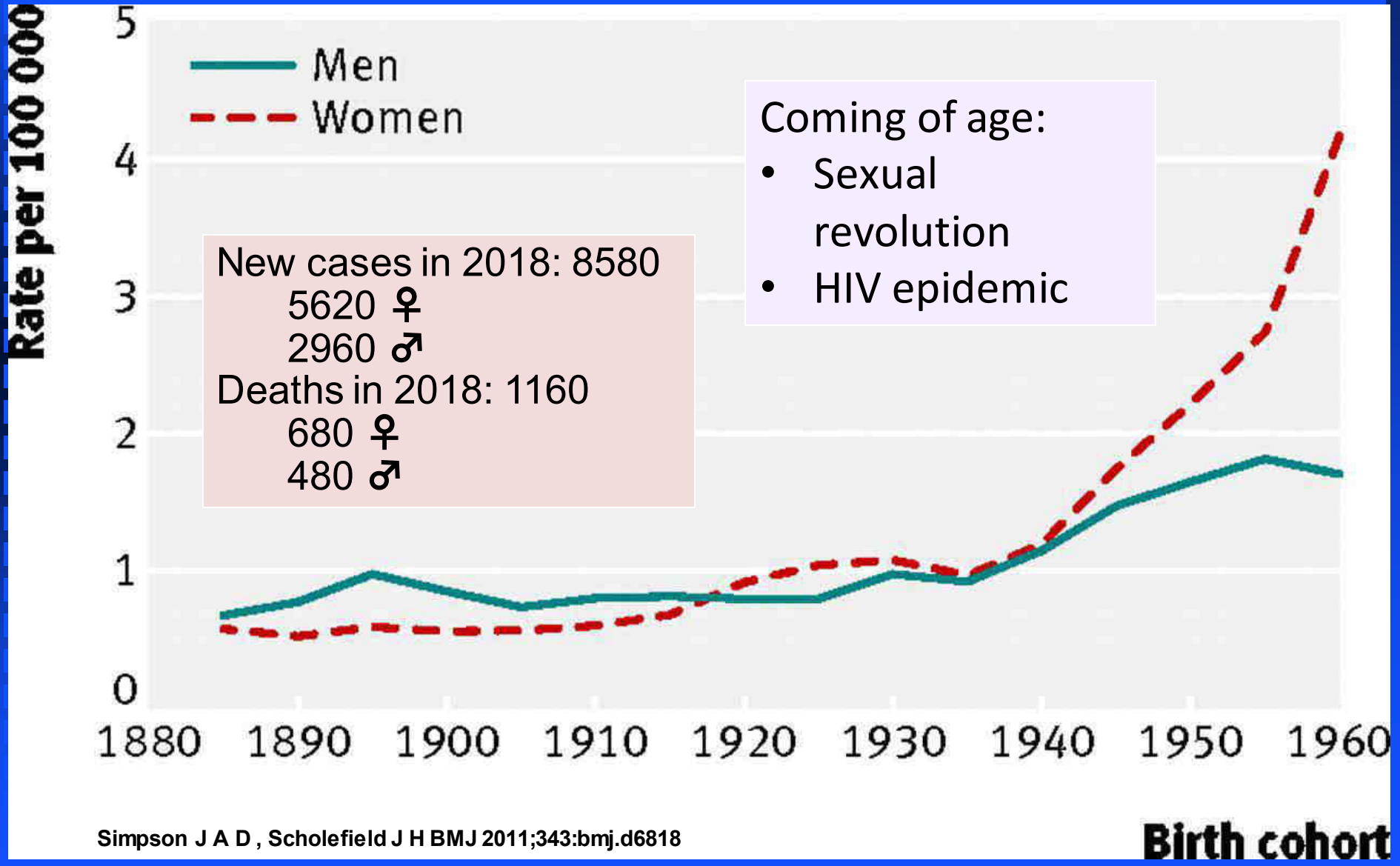




Shiels MS et al. J Natl Cancer Inst 2011;103:753–762
Park LS et al, AIDS 2016, 30:1795–1806


Rectal mucosa
Columns of Morgagni
Levator ani muscle
Dentate (pectinate) line
Deep
External sphincter ani muscles
Subcutaneous
Superficial
Skin
Squamous mucosa

Anal Cancer Rates by Birth Cohort



Simpson J A D , Scholefield J H BMJ 2011;343:bmj.d6818

Anal HPV infection in the Guanacaste cohort

- 31% had any HPV detected in an anal specimen
- The prevalence of anal HPV was higher among women who reported anal intercourse, compared with those who did not (43.4% vs 28.4%; P< .001)

Castro FA et al. J Infect Dis. 2012 Oct 1;206(7):1103-10

Anal HPV infection in the Guanacaste cohort

- Independent risk factors for anal HPV detection among women who reported anal intercourse:
  - cervical HPV (aOR 5.3 [95% CI 3.4-8.2])
  - number of sex partners (aOR, 2.2 [95% CI, 1.1-4.6] for ≥ 4 partners)
  - number of anal intercourse partners (aOR, 1.9 [95% CI, 1.1-3.3] for ≥ 2 partners)
- Independent risk factors for anal HPV detection among women who reported NO anal intercourse:
  - cervical HPV (aOR, 4.7 [95% CI, 3.7-5.9])
  - number of sex partners (aOR, 2.4 [95% CI, 1.7-3.4] for ≥ 4 partners)
  - report of anal fissures (aOR, 2.3 [95% CI, 1.1-4.8])

Castro FA et al. J Infect Dis. 2012 Oct 1;206(7):1103-10

How do women get anal HPV infection?

- Cross-sectional study of women with a previous HPV-mediated gynecologic neoplasia in Tasmania, Australia
- Women presenting for follow-up gynecologic care had anal swab samples taken for anal cytology and HPV genotyping

Simpson S. et al. Cancer Epidemiol. 2016 Jun;42:124-32

How do women get anal HPV infection?

- Of the 123 women tested for HR-HPV DNA, 48 (39.0%) had anal HR-HPV detected
- Front-to-back wiping was associated with significantly increased prevalence of cytological and histological abnormality and HR-HPV carriage/co-carriage (prevalence ratio: 1.99-3.60)
- Dabbing post-toilet was significantly associated with decreased prevalence (PR range: 0.50-0.62)

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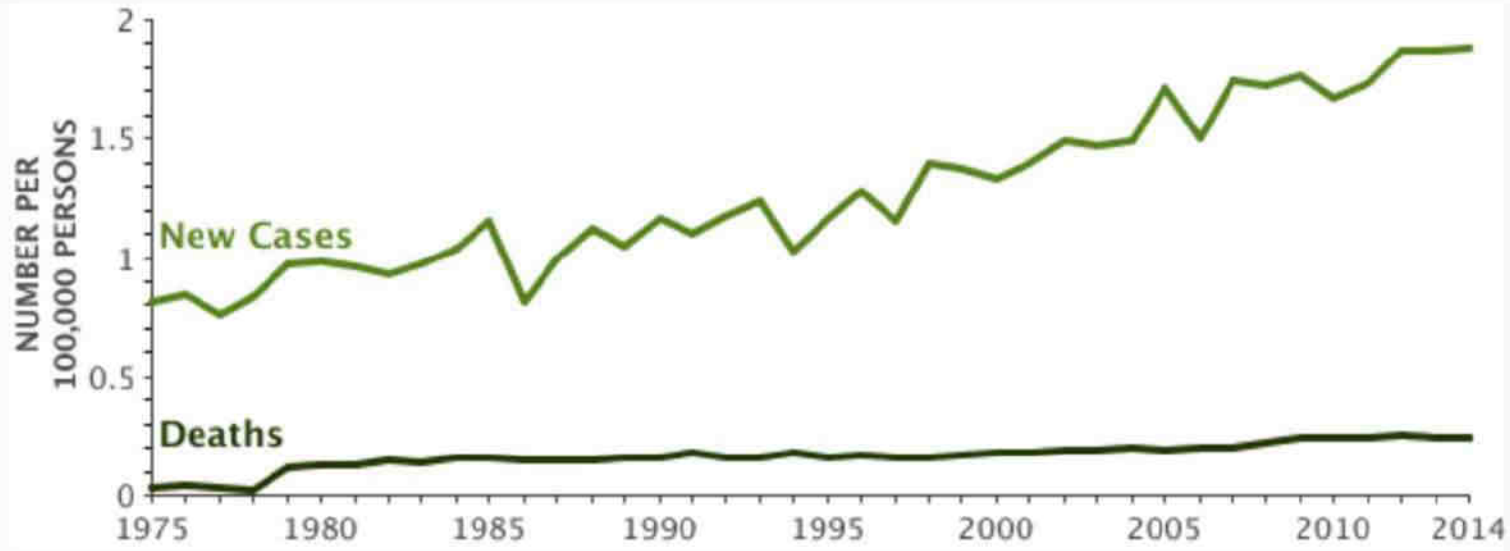
Anal cancer incidence

New Cases, Deaths and 5-Year Relative Survival View Data Table



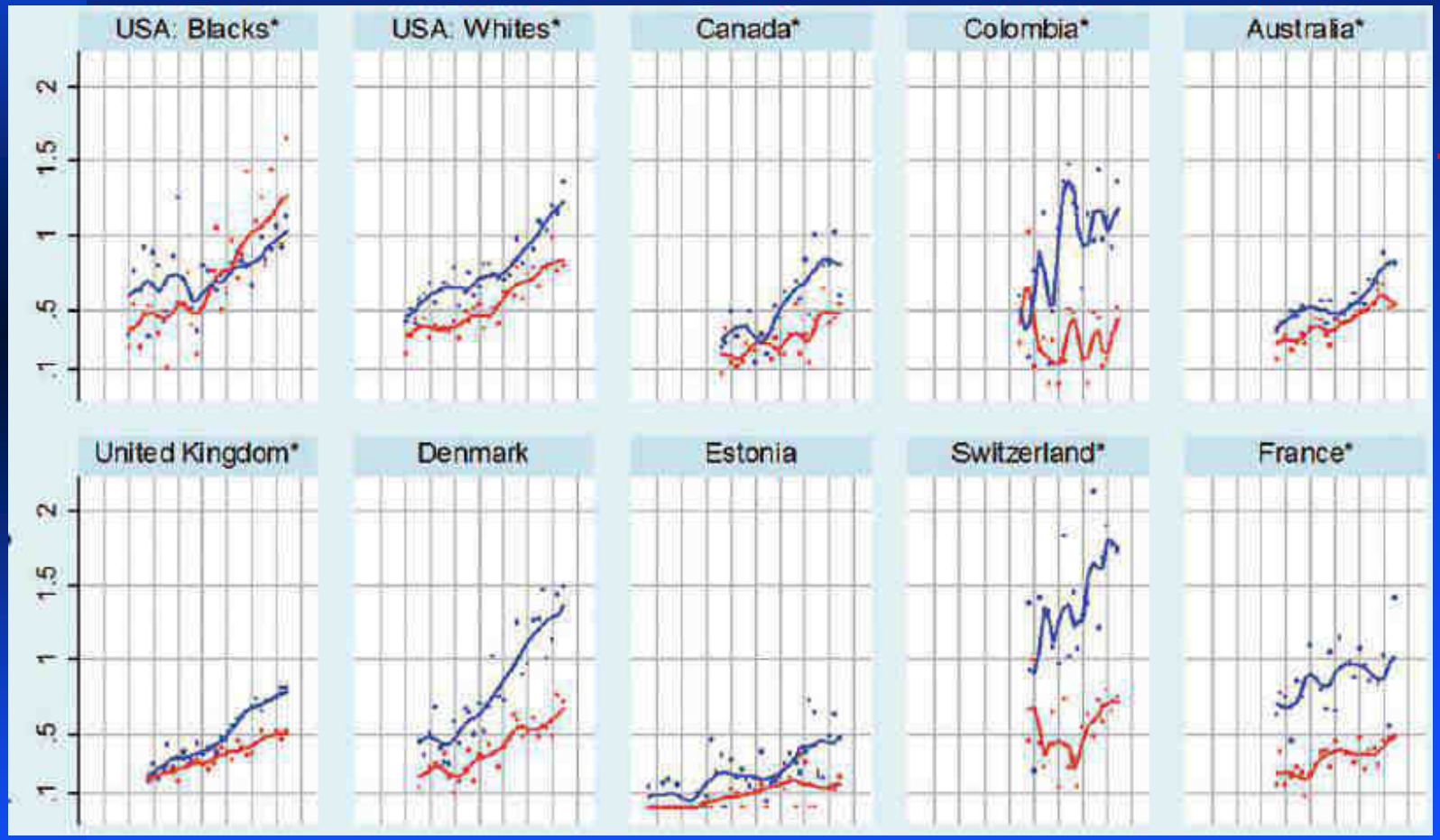
Year	1975	1980	1985	1990	1995	2000	2005	2009
5-Year Relative Survival	64.3%	60.6%	58.1%	57.2%	63.7%	73.2%	67.6%	68.7%

SEER 9 Incidence & U.S. Mortality 1975-2014, All Races, Both Sexes. Rates are Age-Adjusted.

https://seer.cancer.gov/statfacts/html/anus.html

Anal Cancer Incidence Is Increasing In Males and Females in Many Countries

Age-standardized incidence rates of anal squamous cell carcinoma by sex



Based on data from the International Agency for Research on Cancer's Cancer Incidence in Five Continents series.

1. Islami F, et al. *Int J Epidemiol.* 2016 Oct 27. pii: dyw276. [Epub ahead of print].

Anal cancer rates in North American AIDS Cohort Collaboration on Research and Design) (NA-ACCORD) 1996-2007

	Incidence/100,000 (85% CI)
• HIV-infected	
• MSM	131 (109-157)
• MSW	46 (25-77)
• Women	30 (17-50)

Silverberg M et al. CID 2012; 54:1026-34

Recent trends in anal cancer incidence AIDS and cancer registry match study

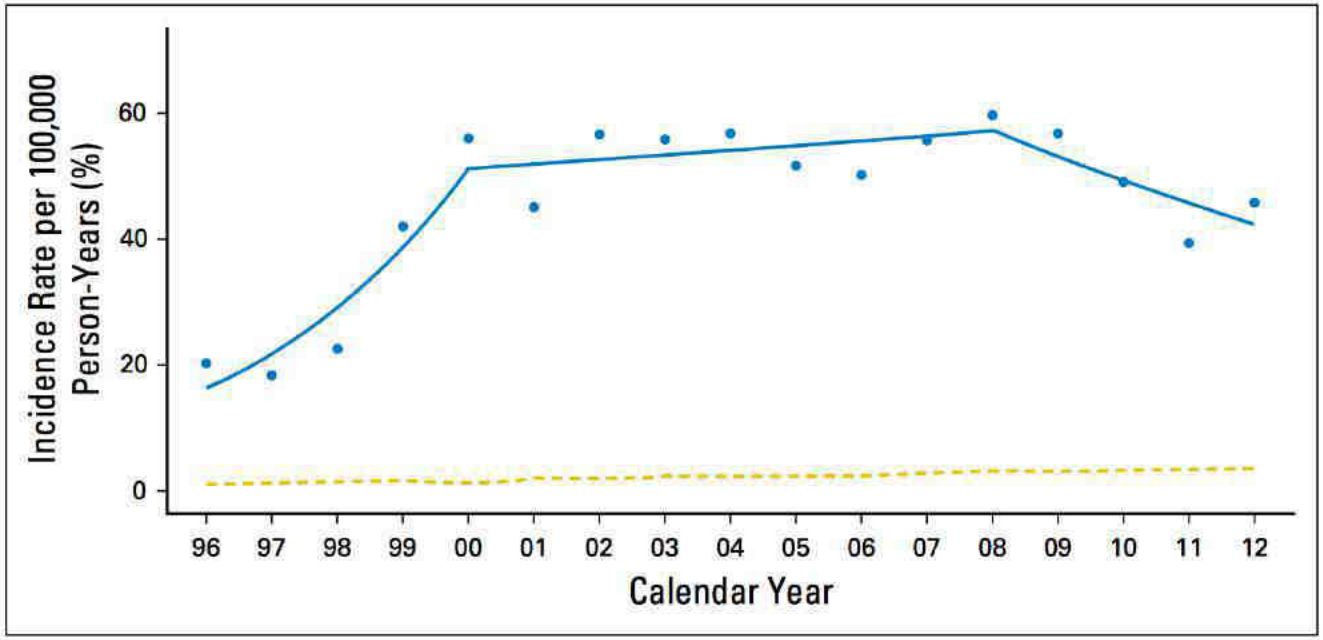
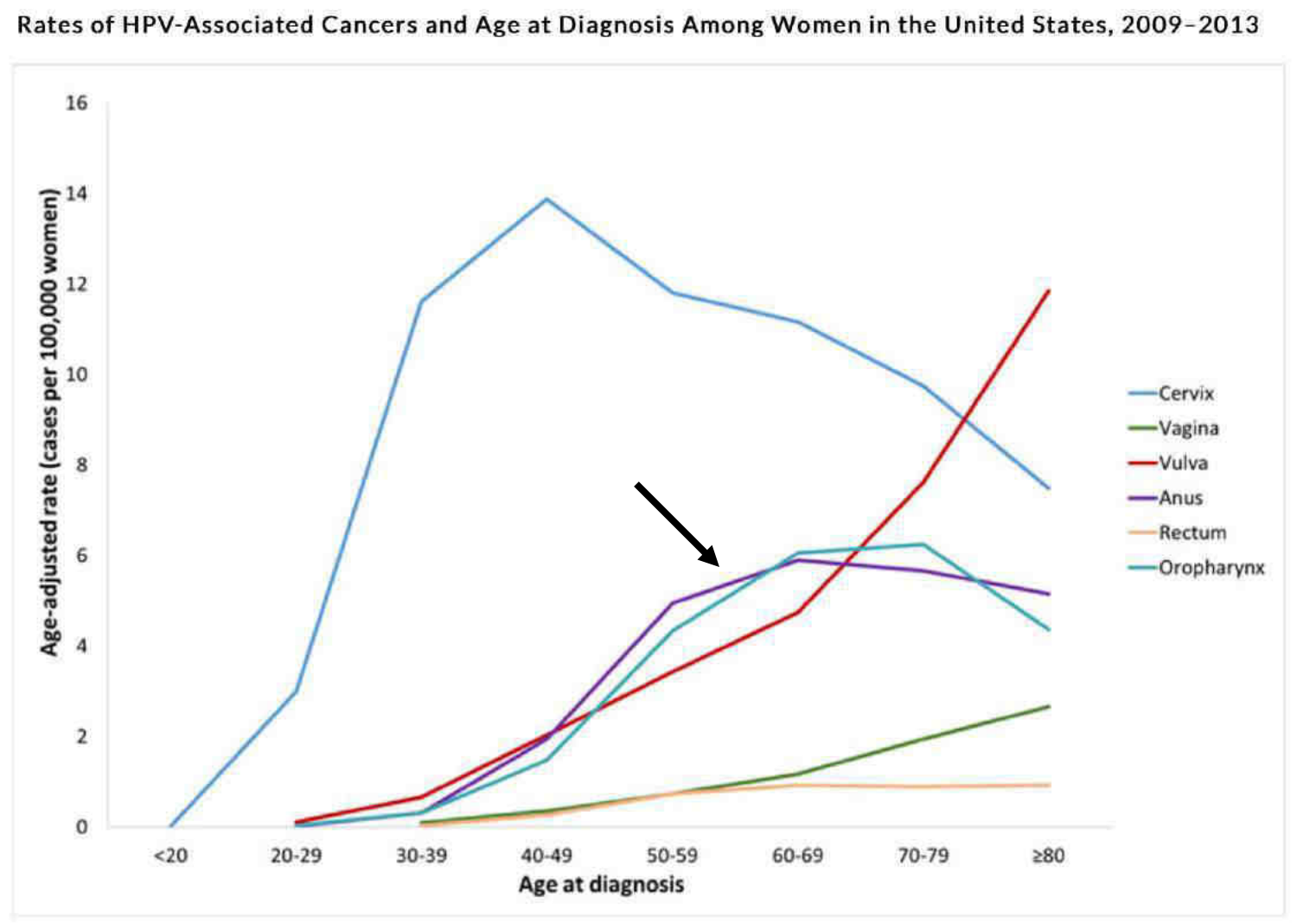


Fig 1. Trend in anal cancer incidence among people with HIV infection and the general population in the United States, 1996 to 2012. Dots indicate the observed incidence of anal cancer among people with HIV in the study population as a function of calendar year. The solid line is the model fitted by Joinpoint, with changes in slope for the incidence trend indicated in 2000 and 2008. The dashed line is the expected incidence in the general population standardized to reflect the demographic characteristics of the HIV population.

Colon-Lopez V. et al J Clon Oncol 2018; 36:68-75

Anal cancer incidence by age-women



https://www.cdc.gov/cancer/hpv/statistics/age.htm, accessed 10-24-17

People living with HIV/AIDS are living into older ages

- In 2015 it was estimated that over half of people living with HIV/AIDS (PLWHA) in the U.S. were over the age of 50 years
- The 2011 CDC HIV Surveillance report estimates that over 311,000 PLWHA were over 50 years old in 2012

Luther VP, Wilkin AM. HIV infection in older adults. Clinics in geriatric medicine. Aug 2007;23(3):567-583, vii.

PLWHA may be aging prematurely

- Several illnesses associated with advanced age are now common among HIV-infected individuals receiving ART
- cardiovascular disease (CVD), liver disease, renal disease, diabetes
- neurocognitive decline and a number of cancers

The future of HPV-related cancer in HIV-infected men and women

	Increased incidence of cancer	Decreased incidence of cancer
Increasing age	Possibly	
Accelerated biological aging	Possibly	
Lower nadir CD4 level	Likely	
Lower current CD4 level	Possibly	
Time on effective ART		Possibly
Earlier initiation of ART		Possibly
Screening for and removal of HSIL		Definitely (cervical) Possibly (anal)
HPV vaccination		Likely (in the future)

Future indicators

- Anal HPV infection
- Anal HSIL

High prevalence of anal HPV infection and HSIL in HIV+ men and women

	Anal HPV prevalence	Anal HSIL prevalence	Anal cancer incidence
HIV-infected MSM	96%	43%	131/100,000
HIV-infected MSW	59%	?	46/100,000
HIV-infected women	90%	28%	30/100,000

Chin-Hong et al. *Ann Int Med.* 2008;149;300-6
Silverberg M et al. CID 2012; 54:1026-34
Conley et al. JID 2010; 202:1567-76
Stier EA et al. Presented at International Anal Neoplasia Society (IANS) Scientific Meeting., San Francisco, CA. November 11-13, 2016

Primary prevention

The nonavalent HPV vaccine

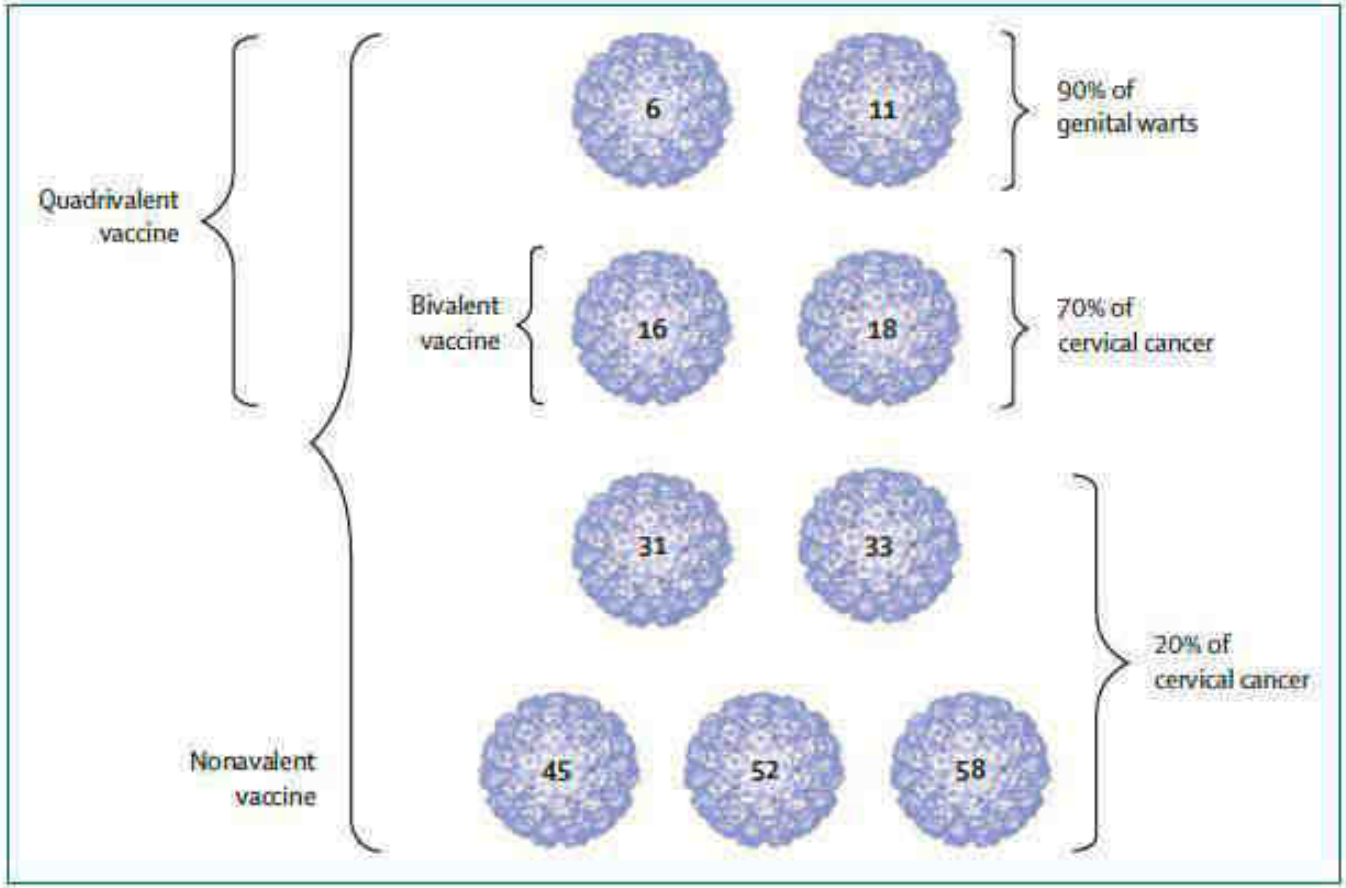


Figure 2: **HPV VLP types in the nonavalent VLP vaccine**
VLPs in the bivalent, quadravalent, and the nonavalent vaccines are shown with the proportion of neoplasistic disease attributed to each group. HPV=human papillomavirus. VLP=virus-like particle.

Schiller J. Lancet Oncol 2015;16(5):e217-25

New ACIP recommendations for HPV vaccine

- For males and females: two injections at least 6 months apart if starting at age 14 or less
- Three injections at 0,1-2 and 6 months if:
  - 15 or older
  - HIV-positive or otherwise immunosuppressed
- One dose under investigation!

ACIP recommendations for HPV vaccine in HIV+ men women

- 9vHPV, 4vHPV or 2vHPV can be used for:
  - Vaccine is safe
  - Produces lower titers than HIV-negative individuals
  - Titers probably adequate but efficacy data are lacking
  - 3 doses for males and females 15, through age 26 years

Vaccination of HIV-positive men and women

- Safe
- Immunogenic
- Effective? (AMC 072, ACTG 5298)

ACIP recommendations for HPV vaccine in HIV+ men women

- 9vHPV, 4vHPV or 2vHPV can be used for:
  - Vaccine is safe
  - Produces lower titers than HIV-negative individuals
  - Titers probably adequate but efficacy data are lacking
  - 3 doses for males and females 15, through age 26 years
  - FDA recently approved vaccination up to age 45 years

Secondary prevention

Who should be screened?

- All HIV-positive men regardless of sexual orientation
- All HIV-negative MSM
- Women with high-grade cervical or vulvar lesions or cancer
- All HIV+ women
- All men and women with perianal condyloma
- Solid organ transplant recipients
- Over 25 years if immunosuppressed, inc. HIV
- Over 40 years if immunocompetent

Treatment of HSIL

- Prevention of anal cancer
- Relief of symptoms

Treatment of anal HSIL

- Challenging due to multifocal nature, size of lesions
- Multiple procedures often needed
- High recurrence rate and incidence of new lesions
- Therapy is primarily ablative
  - hyfrecation/infrared coagulation
- Does it work to prevent anal cancer?

the ANCHOR study.org

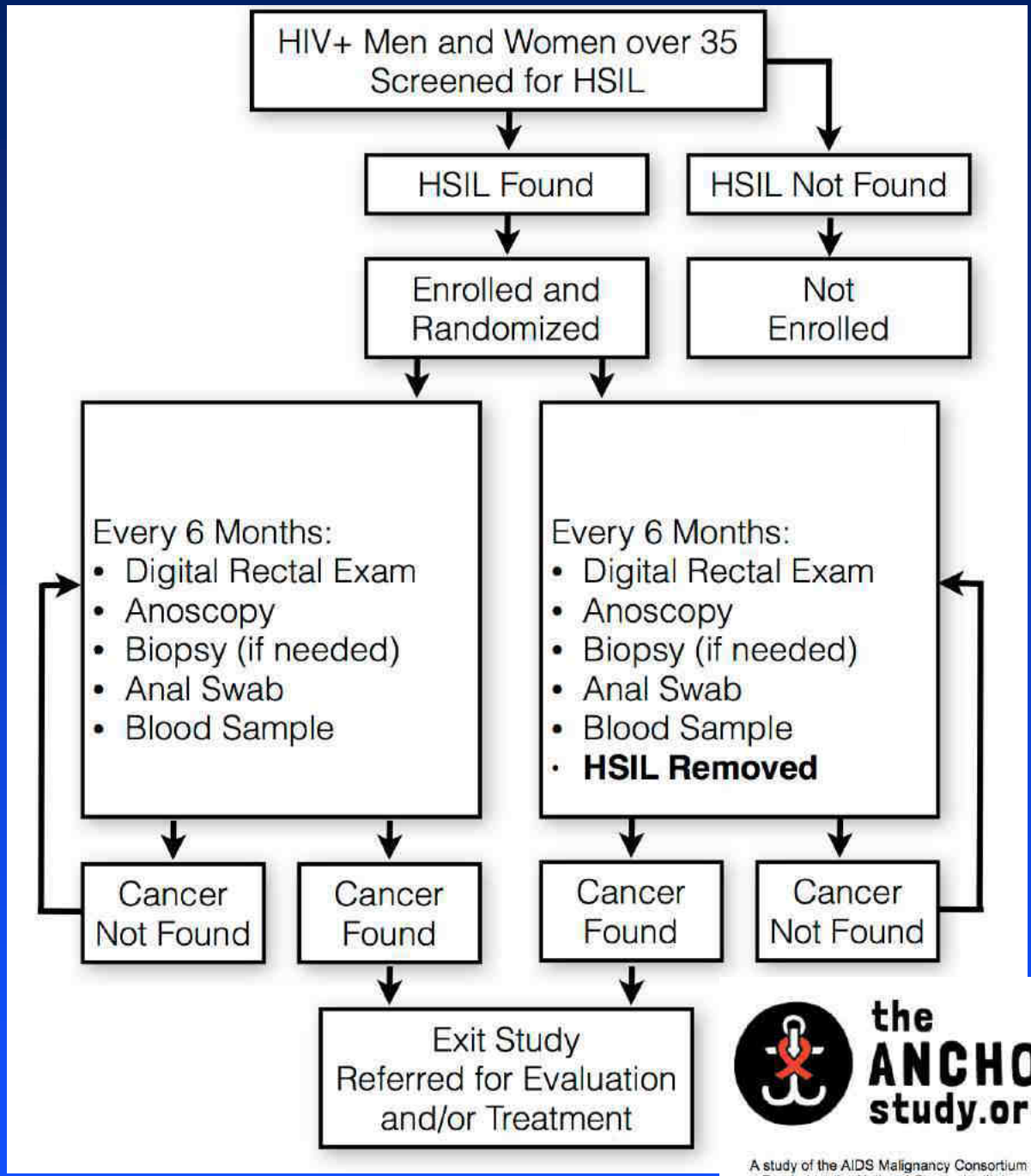
Joel Palefsky, M.D.
Protocol chair

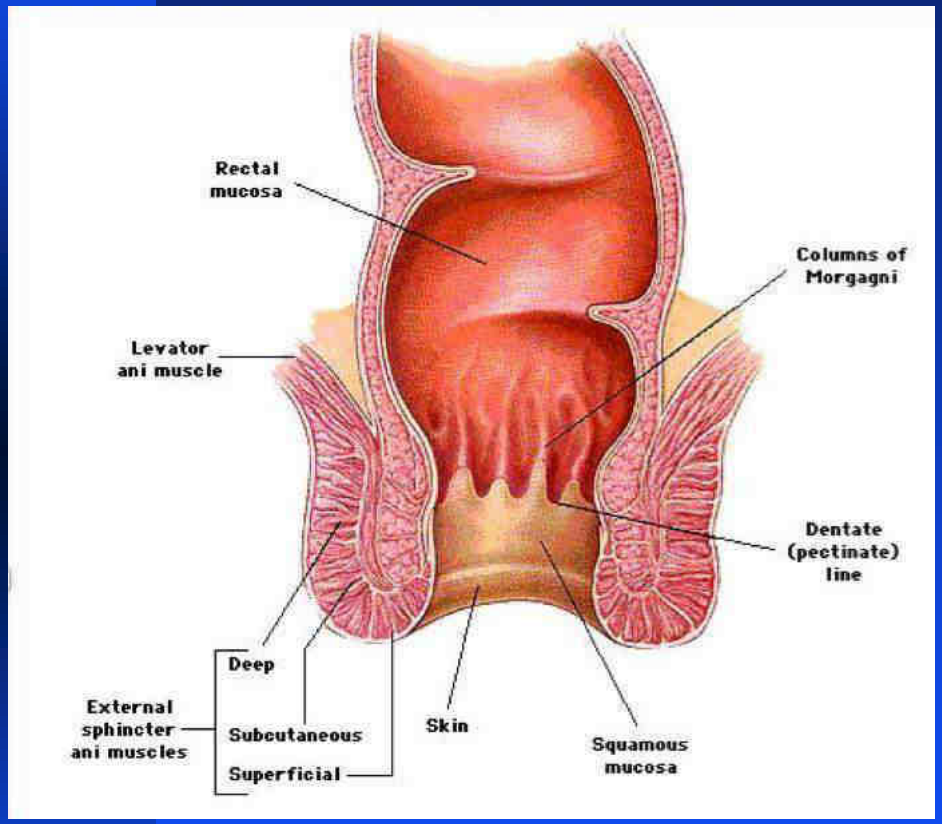
AMC-A01: Funded by NCI and OAR: U01 CA 121947

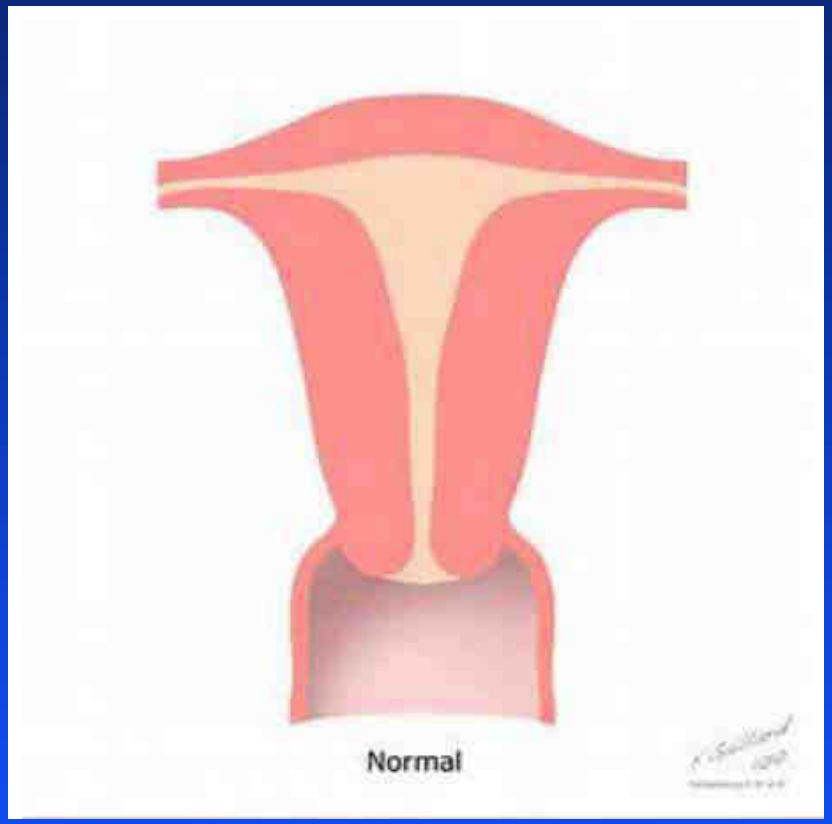
Screen >17,385

Enroll 5,058

Retain for 5 or more years




Rectal mucosa
Columns of Morgagni
Levator ani muscle
Dentate (pectinate) line
Deep
External sphincter ani muscles
Subcutaneous
Superficial
Skin
Squamous mucosa


Normal

Anal vs. cervical cancer pathogenesis

- Rates of anal HPV infection are similar between HIV-infected men and women
- Why is the rate of HSIL lower in women? 30% vs. 50%
- Why is the incidence of anal cancer lower in women? 30/100,000 vs. 131/100,000
- Why is the cancer rate disproportionately high in HIV-infected MSM?

Site specific factors in cancer pathogenesis

- Different microenvironment
  - SCJ with different neighbours
    - Fecal matter, semen

Site specific factors in cancer pathogenesis

- Different sensitivity to hormones
  - Role of estrogen
  - Menstrual cycle
  - Change in TZ with menarche and aging
- Different susceptibility to STIs?
- Different microbiome
  - Gram positive lactobacilli vs. gram-negative

The cervical microbiome and cervical HPV-associated disease

- Two studies of the human cervical microbiome found that differences in Lactobacillus were associated with increased clearance of detectable cervical HPV infection

Brotman, R.M., et al. J Infect Dis, 2014. 210(11): p. 1723-33
Lee, J.E., et al.. PLoS One, 2013. 8(5): p. e63514

The microbiome and anal disease

Table 1: Microbiome Changes Associated with Disease States					
			β-diversity		
	Location	**α-diversity**	**Anti-inflammatory** Firmicutes (*Clostridium*) Bacteroidetes (*Bacteroides fragilis*)	**Inflammatory** Proteobacteria (Enterobacteriaceae)	**Carcinogenic** *Fusobacterium*
IBD	GI tract	Decreased	Decreased	Increased	?
CRC	GI tract	Decreased	Decreased	Increased	Increased
Untreated HIV Infection	GI tract	Variable	Decreased	Increased	?
MSM with HIV (pre-ART)	Anus	Decreased	No statistically significant change	Increased	Increased
Hypothesis:					
HSIL	Anus	Decreased ?	Decreased?	Increased?	Increased?

Summary

- Anal cancer is increasing in general population, will be one of the most common preventable cancers in HIV+ population
- Rates of HPV-related cancer remain high in the ART era where screening and secondary prevention are not practice

Summary

- Issues around aging will become imcreasingly important
- Gender-neutral HPV vaccination is the long-term solution
- Studies of anal cancer offer opportunities to better understand the pathogenesis of cervical cancer

March 4, 2019 is HPV Awareness Day!

www.askaboutHPV.org