

Extra-genital STIs: An update

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Disclosure:

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Off-Label Disclosure

- This presentation will include discussion of the following non-FDA-approved or investigational uses of products/devices:
- Oral and rectal testing for *N. gonorrhoeae* and *C. trachomatis* with:
 - Hologic Gen-Probe APTIMA Combo 2®
 - BDProbeTec™ ET
 - Roche COBAS® PCR

Objectives

- **Review the importance of an accurate and updated sexual history**
- **Discuss methods of testing for extragenital STIs**
- **Review epidemiology of extragenital STIs and pathogens associated with various anatomic sites**
- **Discuss epidemiology of non-cervical HPV**

Important Behaviors to Address

- **Have they engaged in any type of sexual activity?**
- **Number, gender, type and HIV status of sexual partners**
- **Types of sexual activity (oral, vaginal, anal)**
- **Use of barrier methods (condoms, dental dams)**
- **Barriers to safer sexual practices**

CDC. Incorporating HIV prevention into the medical care of persons living with HIV: recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2003; 52(RR-12)

How common are extra-genital sexual behaviors?

- **Males:**

- Active oral

- Lifetime 77%
- Last sex 27%

- Passive oral

- Lifetime 79%
- Last sex 28%

- **Females**

- Active oral

- Lifetime 68%
- Last sex 19%

- Passive oral

- Lifetime 73%
- Last sex 28%

Michael RT, Gagnon JH, Laumann EO, Kolata G. Sex in America: A Definitive Survey. Little, Brown and Co. UK. 1994.

Oral sex amongst UK Youth

Stone et al. *Perspectives on sexual and reproductive health* 2006;38:6-12

- Jan 2003 - May 2005
- Survey of 1,373 young people (58% were 16) attending schools in the UK
- 56% female/44% male/95% heterosexual

	Males	Females
Vaginal sex	42%	52%
Received oral sex (non-virgins)	50%	52%
Received oral sex (virgins)	22%	17%
Condom never used for fellatio	83%	77%

Partner History By Specific Sexual Activities Reported Over 2 Month Period (n = 203 reporting)

Sexual Activity	% Unprotected Partner	% Unprotected Partners HIV Negative or Unknown
Oral Sex	86.0	63.9
Vaginal Sex	25.9	60.0
Receptive Rectal Sex	38.8	48.4
Insertive Rectal Sex	35.1	26.5

Bachmann LH, Grimley DM, Waithaka Y, et al. STD/HIV transmission risk behaviors and STD prevalence among HIV+ men receiving continuing care. *Sex Transm Dis.* 2005;32(1):20-26.

Case

- **49 yo HIV+ male (CD4 410, HIV VL <48) presents for routine HIV f/u visit**
- **Reports 4 days of urethral burning.**
- **3 male partners in previous 2 months.**
 - **HIV+ and HIV- partners; +100% disclosure**
 - **Receptive and insertive anal and oral sex**
 - **Receptive and insertive fisting**
 - **No condoms or gloves**



Case continued...

- **Treatment:**
 - Ceftriaxone 250mg IM x 1
 - Azithromycin 1gm po x 1
- **RPR – nonreactive**
- **GC (pharynx) – positive**
- **GC (urine) – negative; CT (urine) – positive**
- **GC (rectum) – positive; CT (rectum) – negative**
- **Hepatitis C Ab reactive; HCV VL <undetectable**

**He would have been covered
adequately anyway, right?**

But what about the next scenario?

Case



Remainder of exam normal

- **Gram stain: >2PMN/hpf; no GNID**
- **Treatment:**
 - **Azithromycin 1gm po x 1**

Labs

- **CD4 670 (29%); VL 2480**
- **UA – 1.033/mod LE/small bld/4-8 RBC/TNTC WBC; culture negative**
- **Urine CT positive**
- **Oral GC positive**
- **Rectal GC positive, CT negative**
- **RPR 1:32**

Patient returned for treatment of gonorrhea...

And the asymptomatic patient ...

Case

- **25 yo HIV+ male (CD4 890, HIV VL not detected) presents for routine HIV f/u visit**
- **No complaints, routine labs**
- **On Genvoya, adherent**
- **2 male partners in previous 12 months**
 - **No history of sexual contact since his diagnosis (6 months ago)**
 - **1 HIV- partner, 1 HIV unknown**
 - **Insertive and receptive anal sex**
 - **No condoms**

Case

- **Rectal GC negative**
- **Rectal CT positive**
- **Urine GC/CT negative**

- **Returned to clinic for treatment with 1,000 mg azithromycin**
- **RTC in three months and testing not done; 12 month repeat testing negative urine/rectal GC/CT.**

MSM

- **At least annually:**
 - HIV
 - Syphilis
 - Urethral NAAT for gonorrhea and chlamydia
 - Rectal NAAT for gonorrhea and chlamydia (if exposed)
 - Oral NAAT for gonorrhea (if exposed)
 - HbsAg (once then as needed)
 - Hepatitis C Ab (if HIV+)
 - HSV serologies (consider)
- **More frequent testing (q3-6mo) if high risk or STD identified on testing**
- **Vaccinate for Hepatitis A and B and HPV!!**

Performance of NAATs for Diagnosis of Pharyngeal and Rectal Gonorrhea

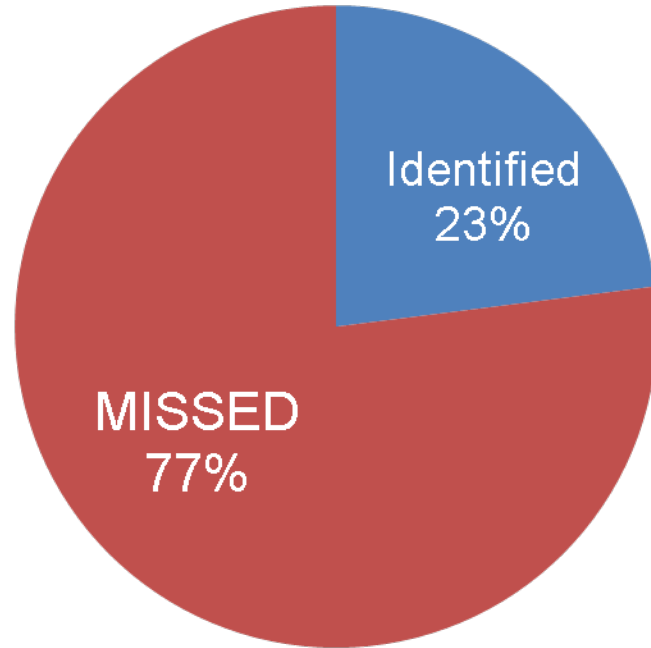
	% Sensitivity		% Specificity	
	<u>phGC</u>	<u>rGC</u>	<u>phGC</u>	<u>rGC</u>
Aptima (TMA)	100%	100%	96%	96%
ProbeTec (SDA)	97%	100%	94%	96%
Amplicor (PCR)	91%	96%	72%	96%
Culture	65%	72%	99%	100%

Bachmann, et al. J Clin Micro. 2009;47:902-907.

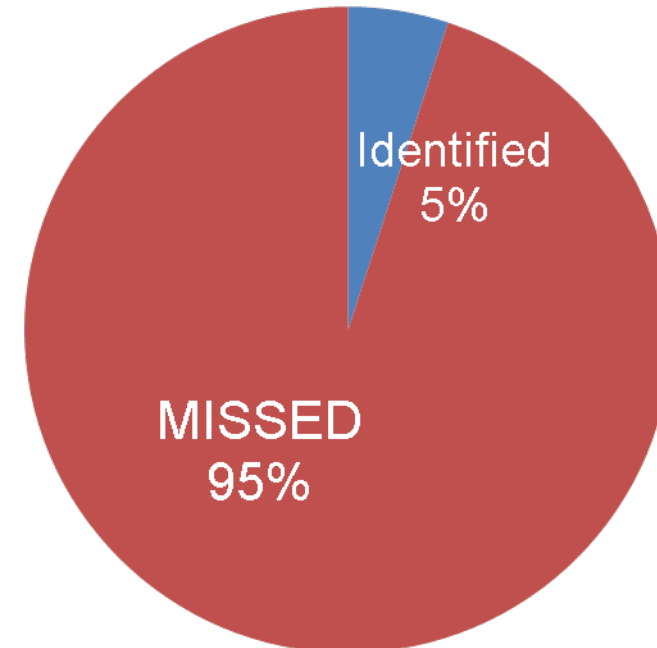
The Catch...

- **NAATs are not FDA-cleared for rectal or pharyngeal specimens**
- **BUT verification testing can be done by labs to meet CLIA requirements**
- **Association of Public Health Laboratories has sample protocols (www.aphl.org)**
- **Two commercial labs (Quest & LabCorp) currently provide GC/CT NAAT for rectal/pharyngeal specimens**

Proportion of CT and GC infections **MISSED** among 3398 asymptomatic MSM if screening only urine/urethral sites, San Francisco, 2008-2009



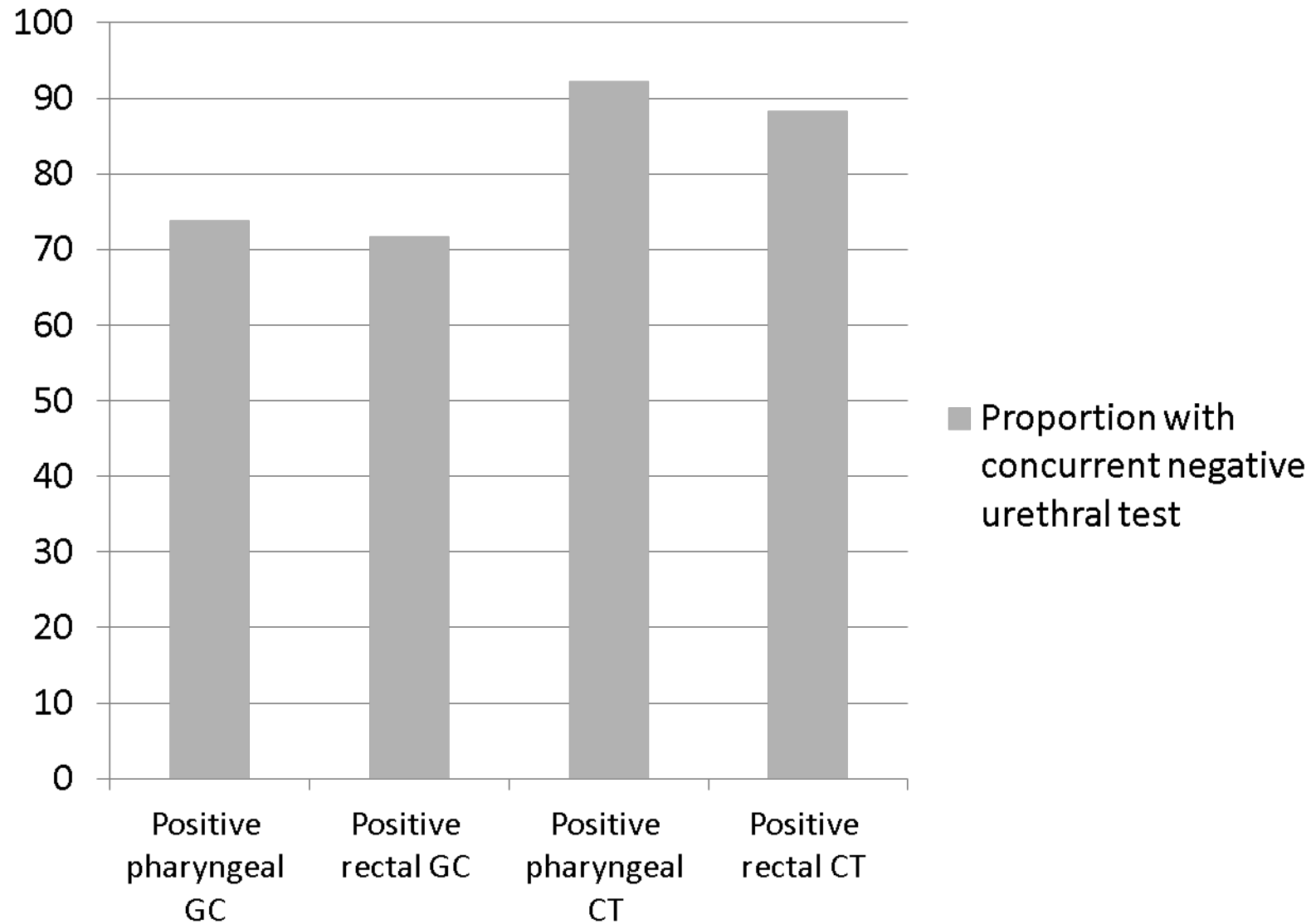
Chlamydia



Gonorrhea

Marcus et al, STD Oct 2011; 38: 922-4

Proportion with concurrent negative urethral test



Patton ME, et al. CID 2014;58(11)1564-70

Do Extra-Genital Infections Matter?

- Jin et al - after controlling for number of episodes of insertive and receptive nonseroconcordant unprotected anal sex, there was an independent association between HIV seroconversion and anal gonorrhea (adjHR = 7.12, 95% confidence interval [CI], 2.05-24.79).
- Pathela et al - 1 in 15 HIV-negative MSM with a documented gonococcal and/or chlamydial rectal infection were diagnosed with HIV within a year. Annual HIV incidence significantly higher among MSM with rectal infections (6.67%; 95% CI, 4.61%–9.35%) than among MSM without rectal infections (2.53%; 95% CI, 1.31%–4.42%).

Jin F, et al. Anal sexually transmitted infections and risk of HIV infection in homosexual men. *J Acquir Immune Defic Syndr*. 2010;53:144–149; Pathela P, et al. HIV incidence among men with and those without sexually transmitted rectal infections: estimates from matching against an HIV case registry. *Clinical Infectious Diseases*. 2013;57(8):1203–9.

PRELIMINARY

COMMUNICATION

JAMA 2013;309(2);163-
170

Neisseria gonorrhoeae Treatment Failure
and Susceptibility to Cefixime in Toronto, Canada

Cephalosporin-Resistant Gonorrhea in North America

2015 STD Treatment Guidelines: Gonorrhea

- **Recommended**
 - **Ceftriaxone 250 mg IM**

Plus (even if chlamydia test negative)

- **Azithromycin 1gm po x 1**

**** Doxycycline 100mg po BID x 7d removed from preferred**

Gonorrhea Treatment Alternatives

Anogenital Infections

ALTERNATIVE CEPHALOSPORINS:

❖ Cefixime 400 mg orally once

PLUS

❖ Dual treatment with azithromycin 1 g orally once, regardless of CT

IN CASE OF SEVERE ALLERGY:

Gentamicin 240 mg IM or 5mg/kg IM + azithromycin 2g PO

OR

Gemifloxacin 320 mg orally + azithromycin 2g PO

Case



- **NH is a 32 yo F with HIV diagnosed in 2004**
 - Stable CD4 ct = 400; VL <50
- **During routine follow-up visit, complains of a rash**
- **Has felt tired lately but otherwise denies specific complaints**

Case continues...

- **Further history reveals that the patient has been sexually active with 5 male partners in the last month.**
- **She does not know that HIV status of her partners**
- **She practices receptive anal sex and oral sex but denies vaginal sex**
- **Condoms for anal sex only**

What is the most appropriate next step?

1. Review medication list
2. Advise to stop using current laundry detergent and follow-up in 1 month
3. Perform an RPR/VDRL, oral testing for *N. gonorrhoeae* and anal testing for *N. gonorrhoeae* and *C. trachomatis*
4. 1 and 3**

Based on the patient's history, where was the likely site of inoculation?

1. Rectum
2. Mouth
3. Vagina
4. Big toe
5. None of the above

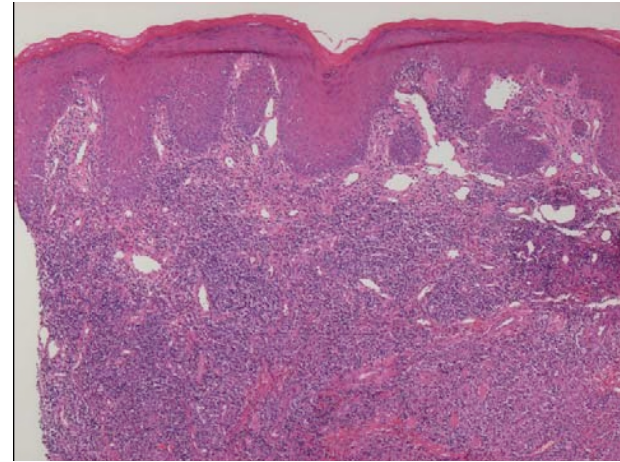
Syphilis

- **Bacterial STD:**
 - Infectious agent: *T. pallidum*
- **Stages:**
 - Primary
 - Secondary
 - Latent stages

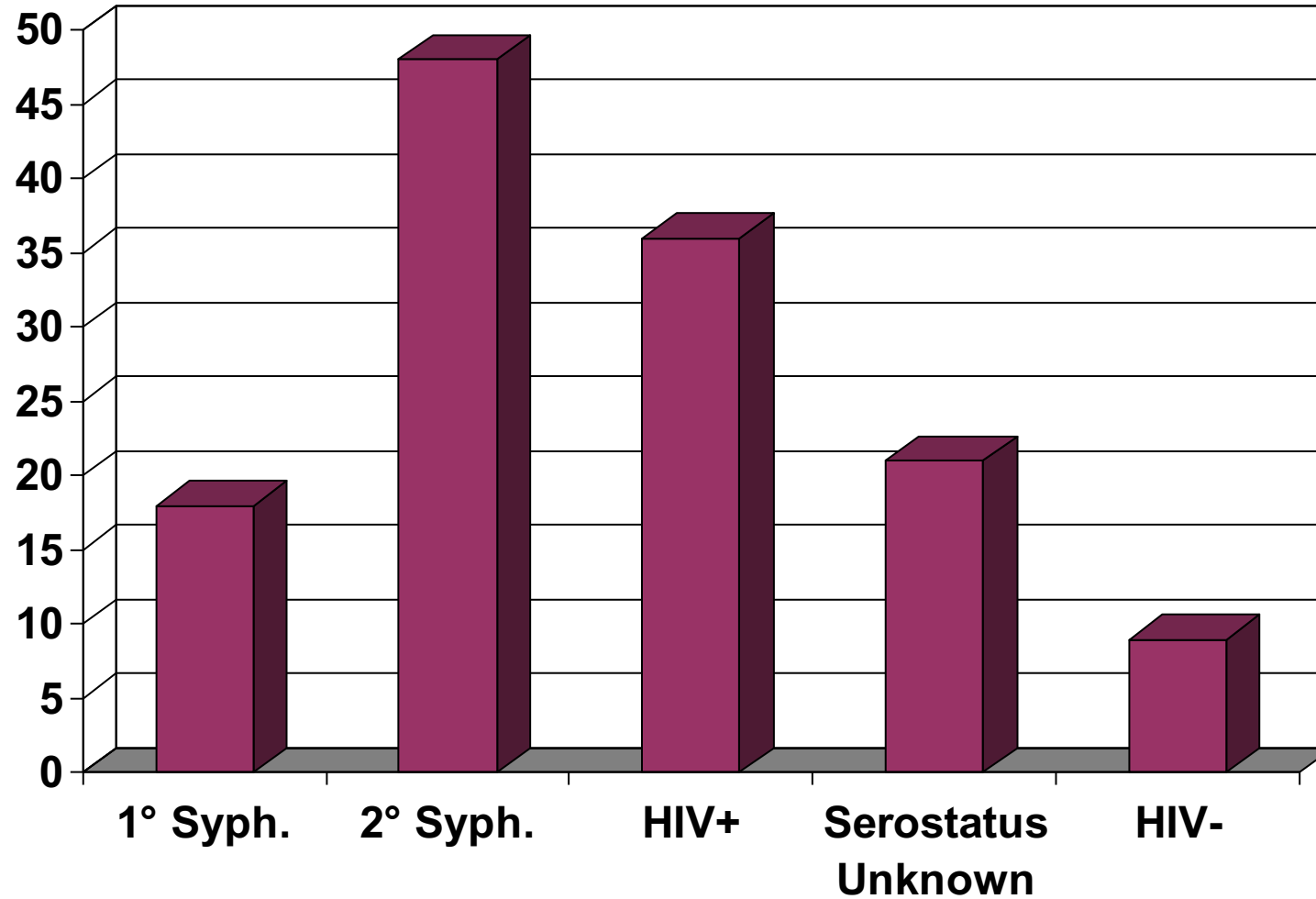




Syphilitic nodules on the tongue
Joan Dalmau, MD et al
J Am Acad Derm



MSM - Oral Sex Only - Chicago, IL 2000-2002



Transmission of primary and secondary syphilis by oral sex --- Chicago, Illinois, 1998—2002. MMWR. October 22, 2004 / 53(41);966-968.

Oral Sex Pathogen Risk

“The only thing you can’t get from oral sex is pregnant.”

... but what are the risks of various STDs?

Oral Sex Pathogen Risk

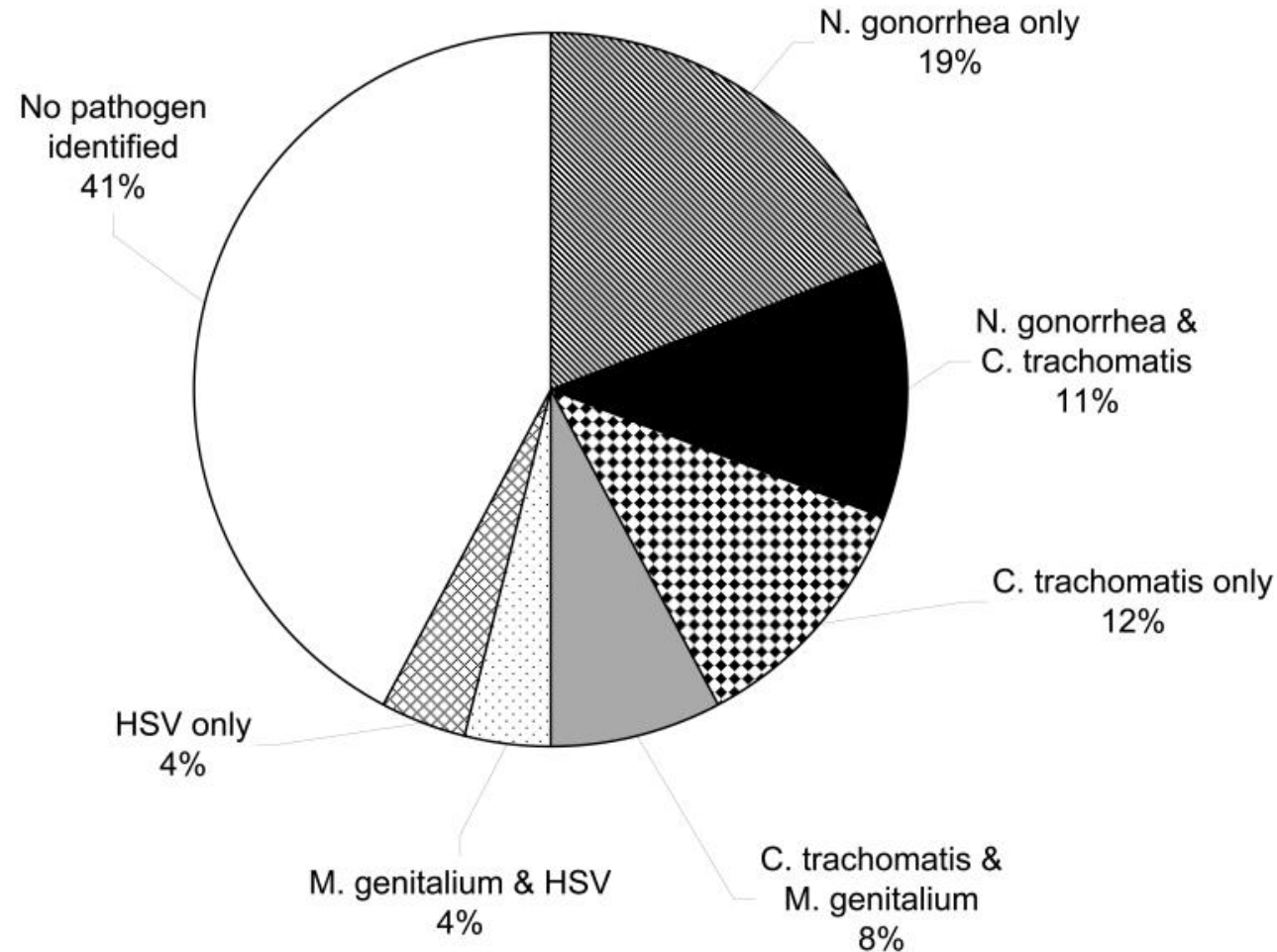
- **Viral (HSV, HPV)**
- **Bacterial (Gonorrhea, Syphilis)**

- **Less risky: Chlamydia (pharyngeal chlamydia, urethral risk less well known), HIV**

Anal Sex Pathogen Risk

- **Viral (HSV, HPV)**
 - **Very prevalent but we don't screen asymptomatic individuals**
- **Bacterial (Gonorrhea, Syphilis, Chlamydia)**
- **HIV efficiently transmitted**
 - **Hep C (HIV positive MSM)**
- **Less risky: Trichomonas (< 0.6%; needs vaginal milieu)**

Anal Sex Pathogen Risk



Who gets Extragenital STIs?

- **MSM**

- Rectal gonorrhea: 5.9%
- Pharyngeal gonorrhea: 4.6%
- Rectal chlamydia: 8.9%

- **Women**

- Rectal gonorrhea: 1.9%
- Pharyngeal gonorrhea: 2.1%
- Rectal chlamydia: 8.7%

- **MSW**

- Rectal gonorrhea: 3.5%
- Pharyngeal gonorrhea: 2.2%
- Rectal chlamydia: 7.7%

← Identity vs. behavior

Oral HPV



Epidemiologic Breakthrough!

"No. Because without wanting to get too specific, *this particular cancer is caused by HPV*, which actually comes about from cunnilingus, ... But yeah, *it's a sexually transmitted disease that causes cancer.*"

- Michael Douglas

Oral Cancer and HPV

- **Associated with better prognosis**
- **HPV tumor status is the strongest individual predictor of survival**
 - **30% absolute increase**

Gillison ML, *et. al.* Human Papillomavirus and Diseases of the Upper Airway: Head and Neck Cancer and Respiratory Papillomatosis, Vaccine 2012.

Oral HPV

- **Increasingly recognized as a cause of a subset of SCC of the oral cavity**
 - Oral Cavity 23%
 - Oropharynx 35%
 - Tonsillar 90%
- **Heavily influenced by birth cohort effect**
 - Lower age
 - Gender

Oral Cancer and HPV



Sites most likely to be HPV-related include subsites of the Waldeyer ring, including the soft palate, palatine and lingual tonsils

Head and Neck Cancer - Epidemiology

- **Estimated 49,260 new cases of HNC diagnosed in US in 2010**
- **Incidence higher in males vs females**
- **Median age 7th decade though lower for cancers of the tonsil (57 years)**
- **Incidence of tongue and tonsillar malignancies increasing in several countries compared to decreases in other oral cancers over same timeframe**

What's the Fraction?

- **Oropharyngeal cancers (OPC) attributable to HPV globally ~ 26%**
 - **More developed countries (North America, Japan, Australia): ~50%**
- **Inversely correlates with rates of smoking in the population**
- **Contributes more to OPC in men than women**
- **HPV 16: >80% of HPV positive OPCs**

Giuliano AR, et.al. **EUROGIN 2014 roadmap: Differences in human papillomavirus infection natural history, transmission and human papillomavirus-related cancer incidence by gender and anatomic site of infection.** Int J Cancer. 2014 Jul 17

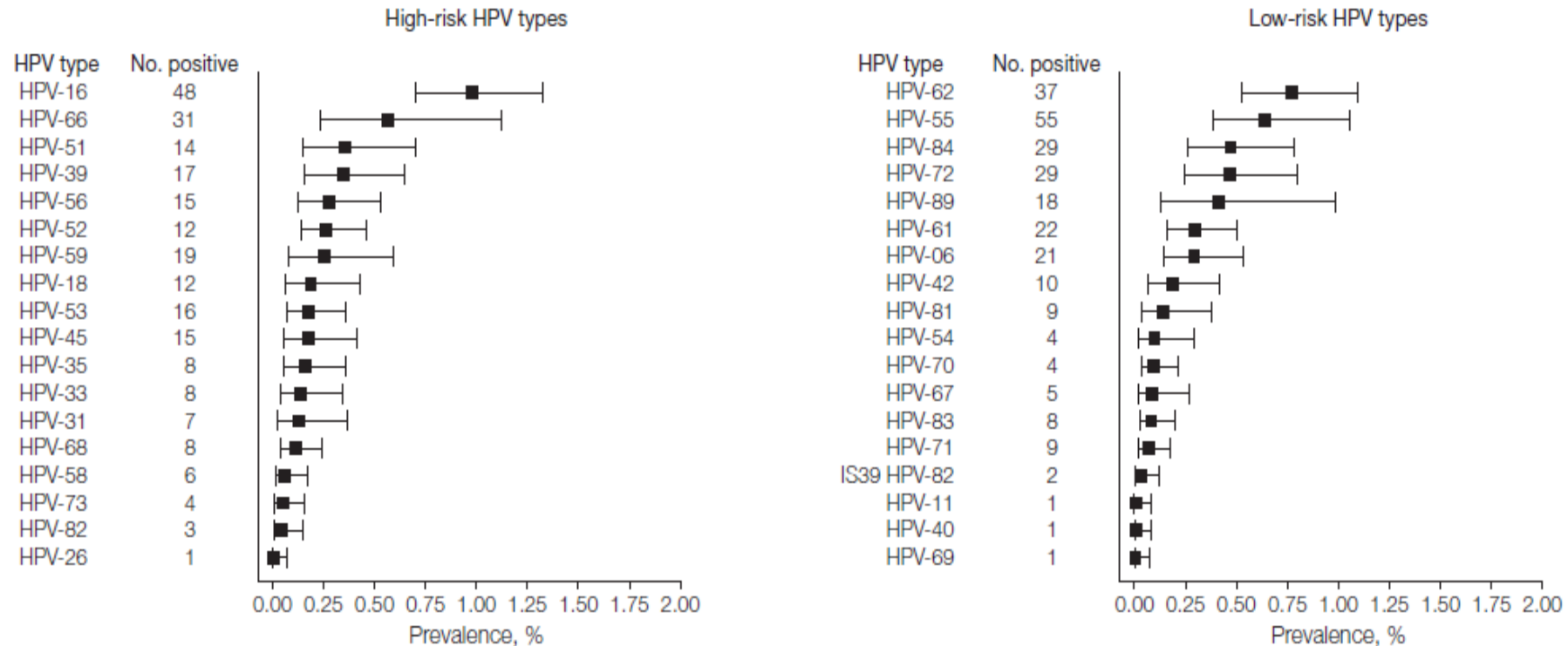
Ndiaye C, et.al., **HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis.** Lancet Oncol. 2014 Nov;15(12)

Risk Factors for HPV-Head and Neck Squamous Cell Carcinoma (HNSCC)

- **Young age**
- **More likely to have higher SES**
- **More likely to have higher education**
- **More likely to have more lifetime sexual partners**
- **Associated with white race**
- **More likely to be diagnosed at later stage though survival better**

Prevalence of Oral HPV Infection in the United States, 2009-2010

Figure 1. Prevalence of Oral HPV Infection by Individual Genotypes in the US Population Aged 14 to 69 Years



The weighted prevalence (and 95% CI) for each of the 37 human papillomavirus (HPV) types evaluated is stratified by classification as high-risk or low-risk HPV types based on epidemiological associations with cervical cancer. HPV type 64 was not detected. The data are derived from the 5501 NHANES participants with evaluable samples. Error bars indicate 95% CIs.

Overall prevalence 6.9% (3.7% HR and 3.1% LR)!!; Gillison ML. JAMA 2012; 307: 693-703

Oral HPV prevalence and incidence

- **Male university students (18-25yo), non-HIV infected, sexually active with women:**
 - Prevalence oral HPV at enrollment – 7.5%
 - 12mo cumulative incidence – 12.3% (95% CI 7.0-21.3)
 - Prevalence HPV-16 – 2.8%
 - 12mo cumulative incidence HPV-16 – 0.8% (95% CI 0.1-5.7%)
 - None of the incident and 28.6% of prevalent oral HPV detected more than once

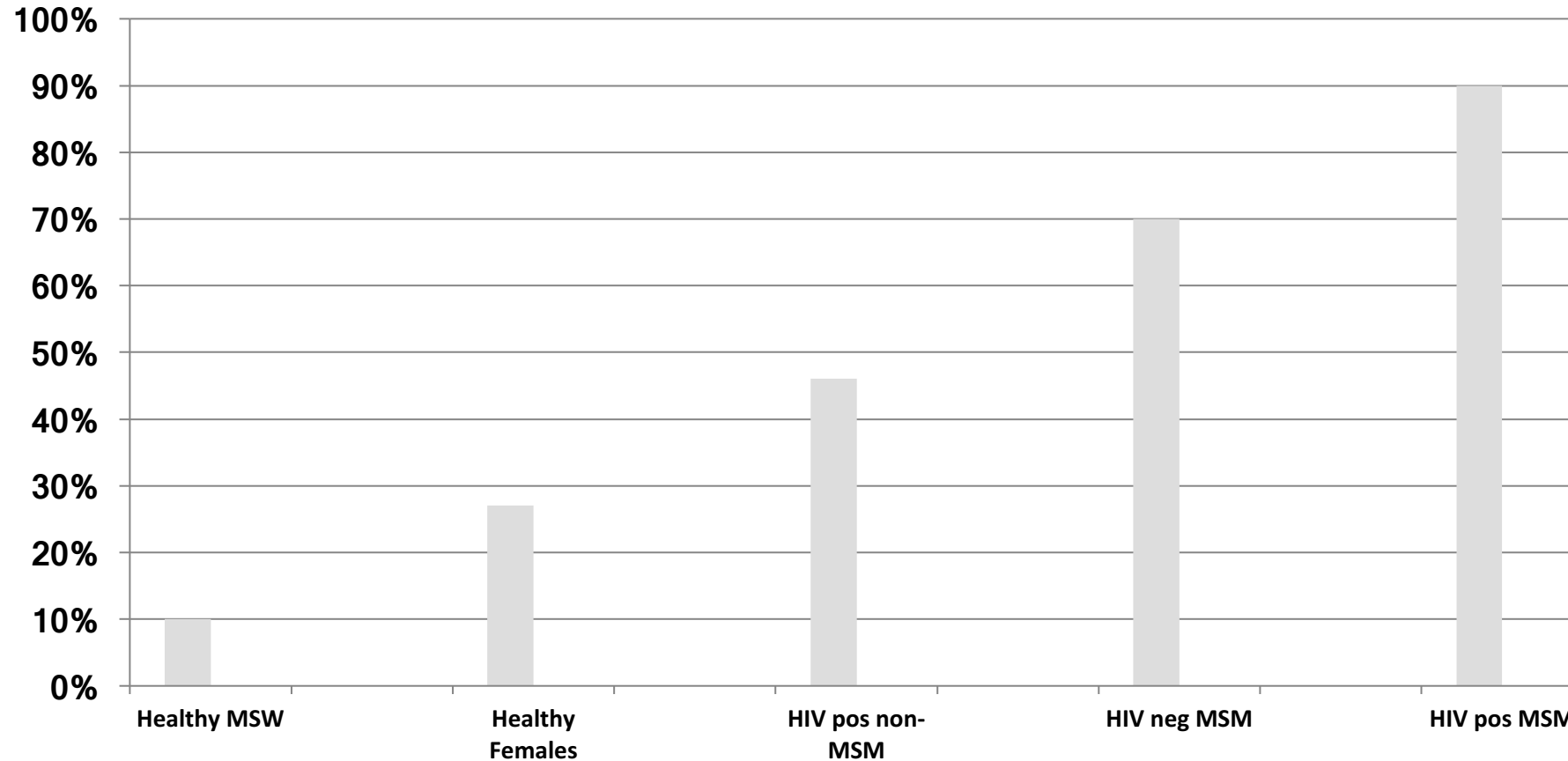
Factors Independently Associated with Oral HPV Infection:

- **Age – bimodal distribution for men with peak prevalence 55-64yrs**
- **Sex – Males 3-fold higher than females**
- **Lifetime # sex partners – vaginal or oral sex**
- **Current smoking intensity – for F>M**

Prevalence of Cervical and Oral Human Papillomavirus Infections Among US Women

- NHANES 2009-2010
- Prevalence of HPV infection among women 42.7% in the cervix and 3.8% in the oral cavity
- Prevalence of oral HPV 5-fold higher in women with cervical HPV compared to women without cervical HPV (7.0% vs 1.4%; PR 4.9; 95% CI 2.7-8.7)

Anal HPV Infection is Common



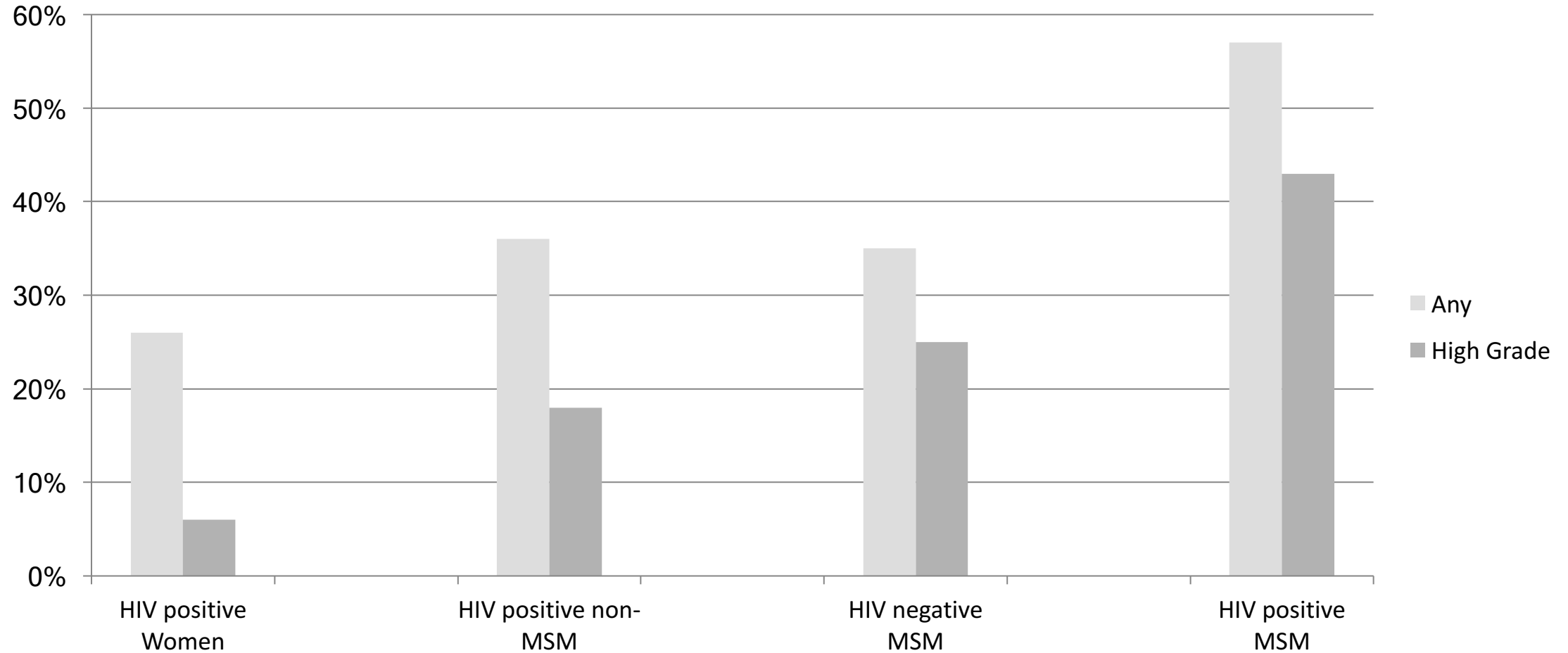
Chin-Hong, *et. al.* , The Journal of infectious diseases, 2004

Nielson, C.M., *et.al.* Cancer epidemiology, biomarkers & prevention, 2009

Ostor, A.G. International journal of gynecological pathology ,1993

Hernandez, B.Y. *et. al.*, Cancer epidemiology, biomarkers & prevention, 2005

ANAL DYSPLASIA IS COMMON



Chin-Hong PV, *et.al.* Comparison of patient- and clinician-collected anal cytology samples to screen for human papillomavirus-associated anal intraepithelial neoplasia in men who have sex with men, *Ann.Intern.Med.*, 2008.

ANAL CANCER INCIDENCE: NA-ACCORD

- **HIV positive MSM: 131**
- **HIV positive non-MSM: 46**
- **HIV positive Women: 30**

- **HIV negative men: 2**

Silverberg MJ, *et.al.*, Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America, *Clin.Infect.Dis.*, 2012

Anal Cancer Statistics

- **Estimated new anal cancer cases in U.S. (2014): 7210**
- **Estimated deaths from anal cancer in U.S. (2014): 950**
- **0.4% of all cancers diagnosed in the U.S. in 2014**
- **Anal Cancer rates have increased by ~2%/yr since the 1970's**
- **Incidence of SCCA among men in general population (~0.8/100K) vs HIV-infected MSM (~70/100K)**

Risk Factors for Anal Cancer

- **High risk HPV*******
- **HIV infection**
- **Multiple sex partners**
- **Multiple HPV strains**
- **Smoking**
- **Immunosuppression**

What do we know?

- **Anal cancer survival significantly improved for patients who receive a diagnosis of local disease (5-year survival – 78%) vs regional disease (56%) vs distant disease (18%)**
- **We do not know the natural history of anal dysplasia**
- **We do not know if screening individuals with anal Pap smears lead to improved outcomes**

Conclusion

- **Orientation ≠ Behavior**
 - Ask
- **Extragenital sexual activity is very common**
 - Test
- **Most STIs are asymptomatic**
 - Treat
- **HPV is ubiquitous and common in several non-cervical locations**

Questions?