STDS AND HIV

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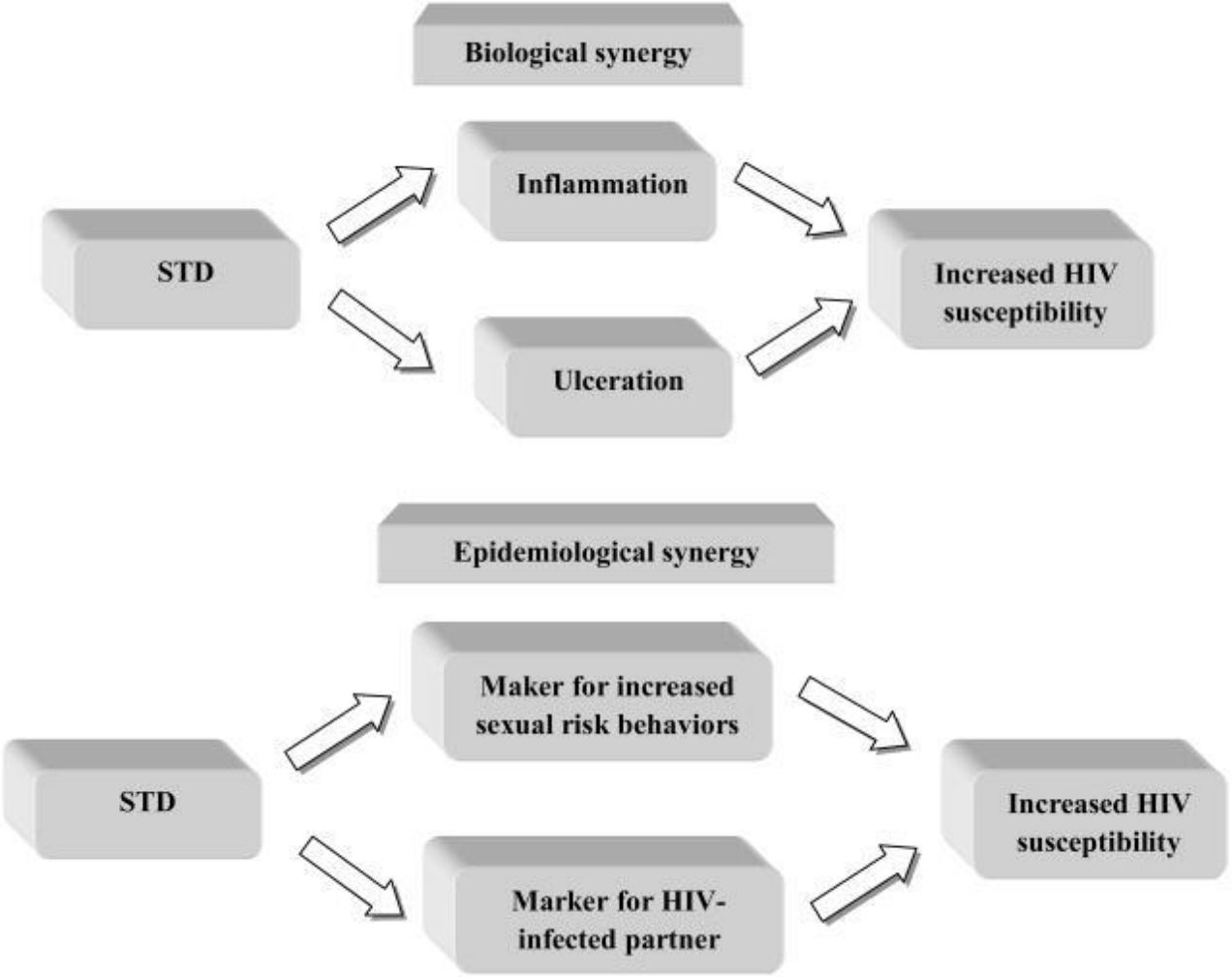
Objectives

- By the end of this lecture, participants will be able to:
  - Identify the impact of STDs on HIV acquisition and transmission.
  - Describe the epidemiology of STDs among HIV-infected patients
  - Describe the guidelines for STD screening among HIV-infected patients
  - Identify special considerations for the diagnosis and treatment of STDs in HIV-patients

STDs and the risk of HIV acquisition

STDs and HIV transmission



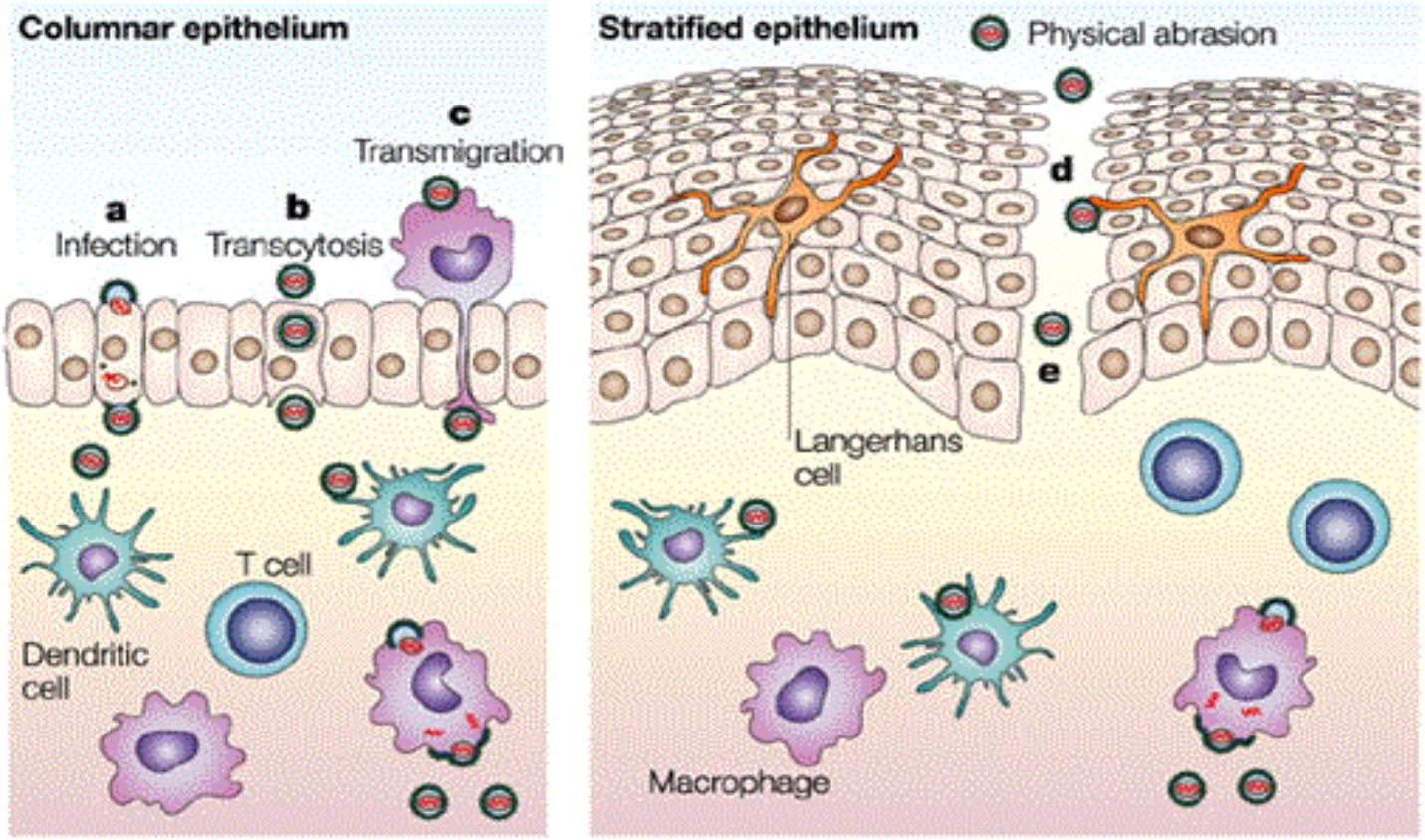
Mayer et al, Am J Reprod Immunol, 2011

Primary prevention: STDs increase risk of acquisition of HIV

- Reduce physical/mechanical barriers to transmission (e.g. ulcerations in mucosa)
- Increase the numbers of receptor cells or density of receptors (persistent inflammation)
- Produce a vaginal environment that is more conducive to HIV transmission (e.g. anaerobic environment from BV)

Cohen et al, Topics in HIV, 2004

HIV sexual transmission on cellular level



Shattock et el, 2003

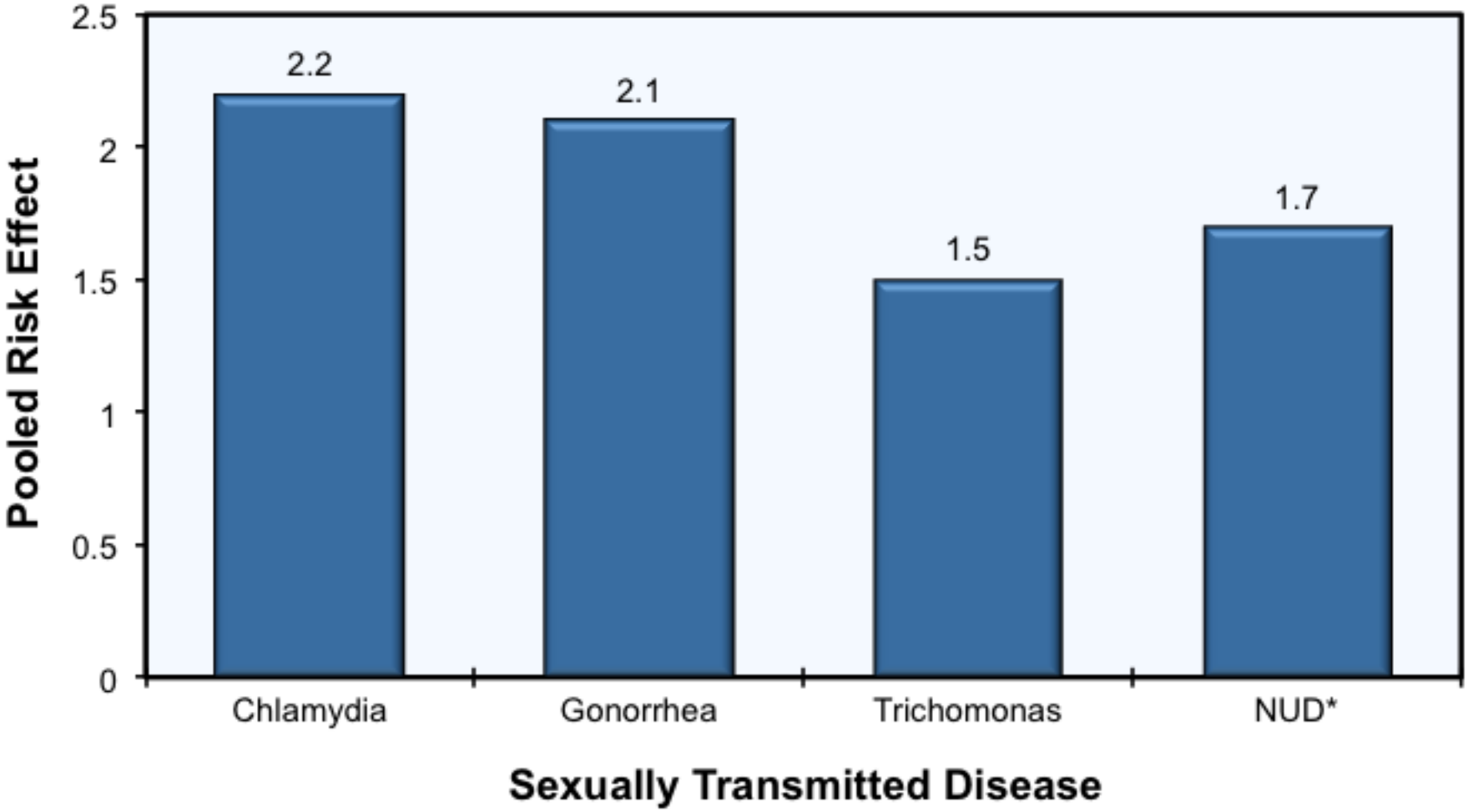
Types and Characteristics of STDs

Table 2 | **Types of sexually transmitted infections**

Characteristics	Aetiological agents
Systemic infections without mucosal disease	HIV, hepatitis B, cytomegalovirus
Genital ulcers	*Haemophilus ducreyi*, herpes simplex virus 1 and 2, *Treponema pallidum*
Mucosal inflammation	*Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis*
Changes in epithelial cells	Human papillomavirus

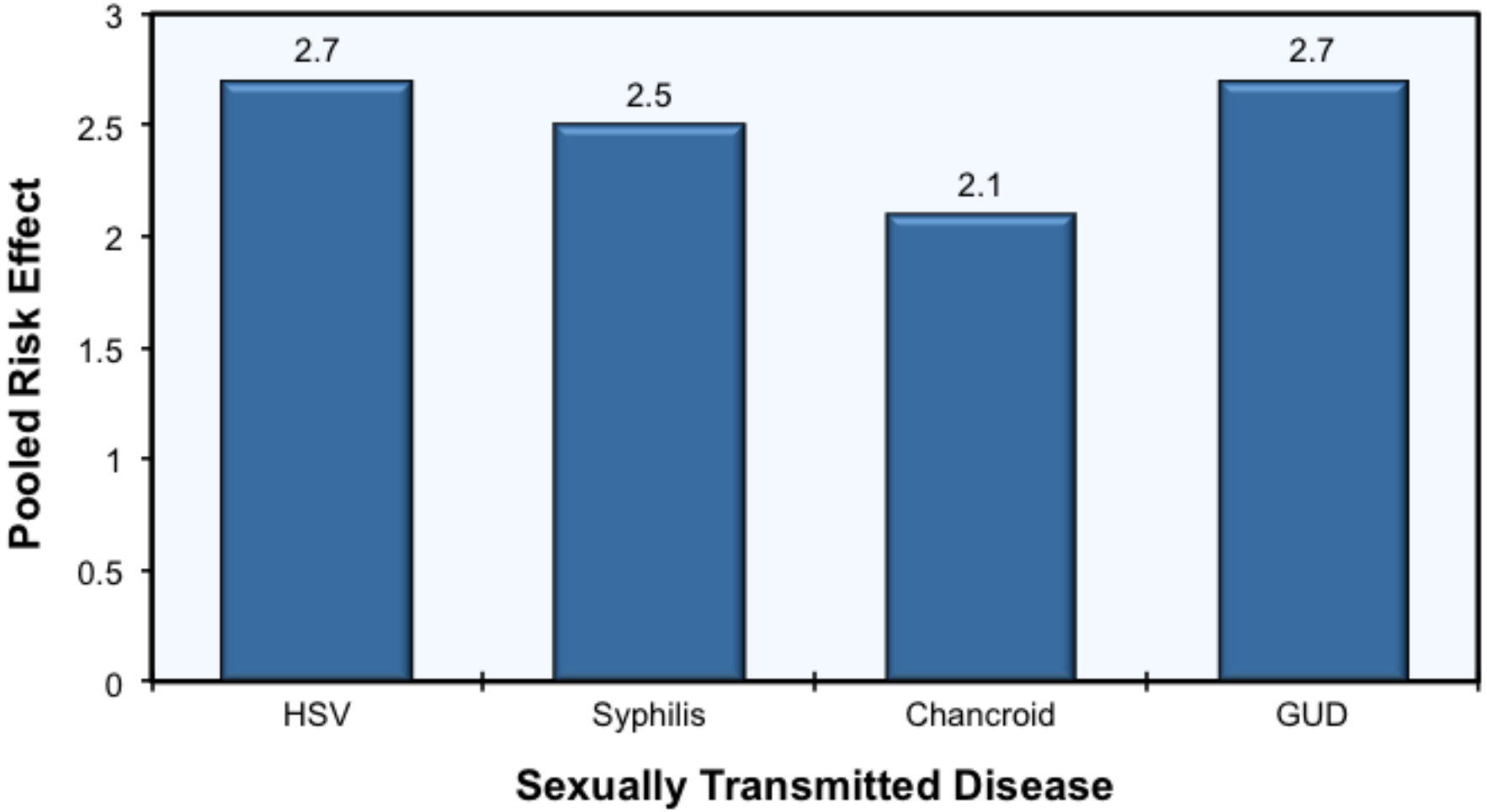
Galvin and Cohen, Nature Reviews Micro, 2004

Pooled Risk Effect of Non-Ulcerative STDs on Susceptibility to HIV



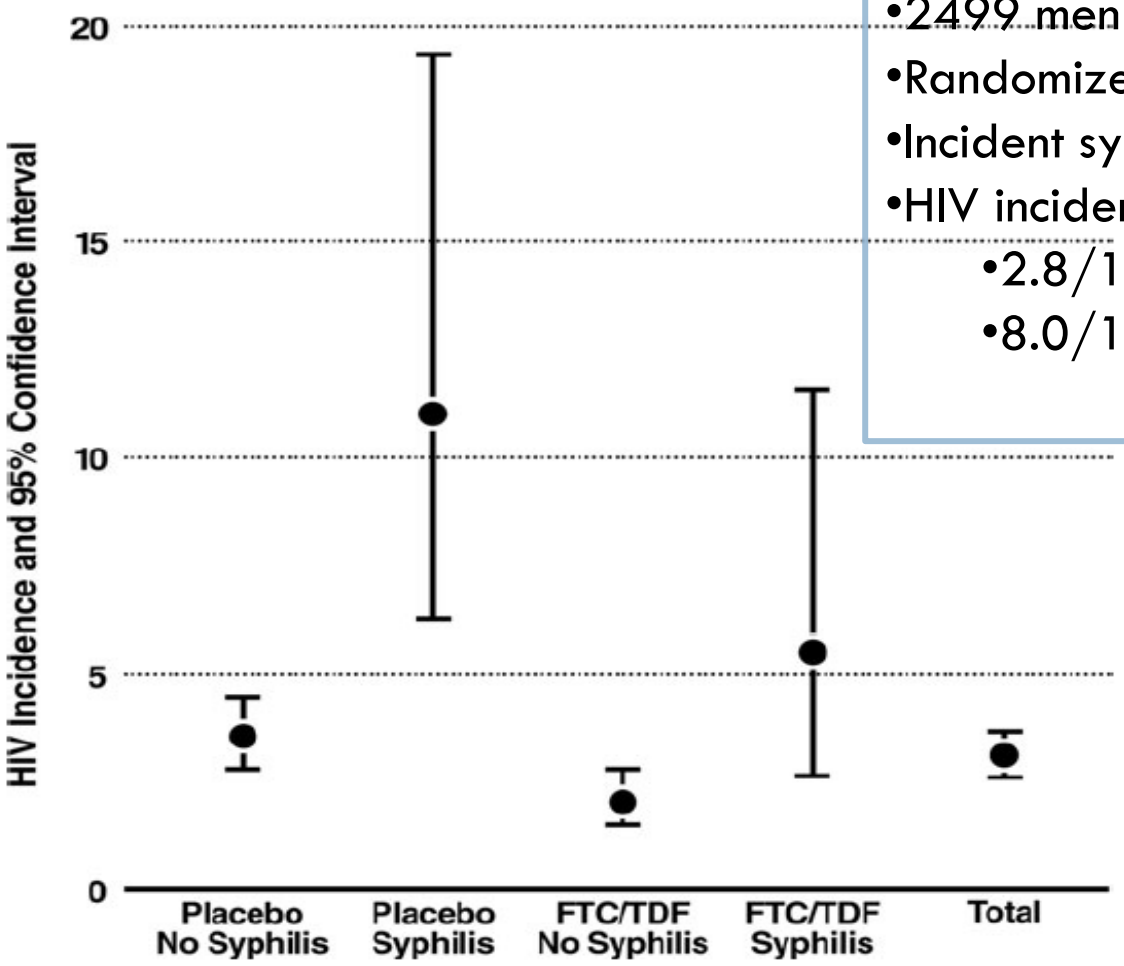
Rottingen, STD, 2001

Pooled Risk Effect of Genital Ulcer Diseases on Susceptibility to HIV



Rottingen, STD, 2001

HIV Incidence According to Incident Syphilis and Treatment Arm, iPrex study



- 2499 men and transgender women
- Randomized to TDF/FTC v placebo
- Incident syphilis rate was same
- HIV incidence:
  - 2.8/100py in no syphilis group
  - 8.0/100py in syphilis group

Solomon, CID, 2014

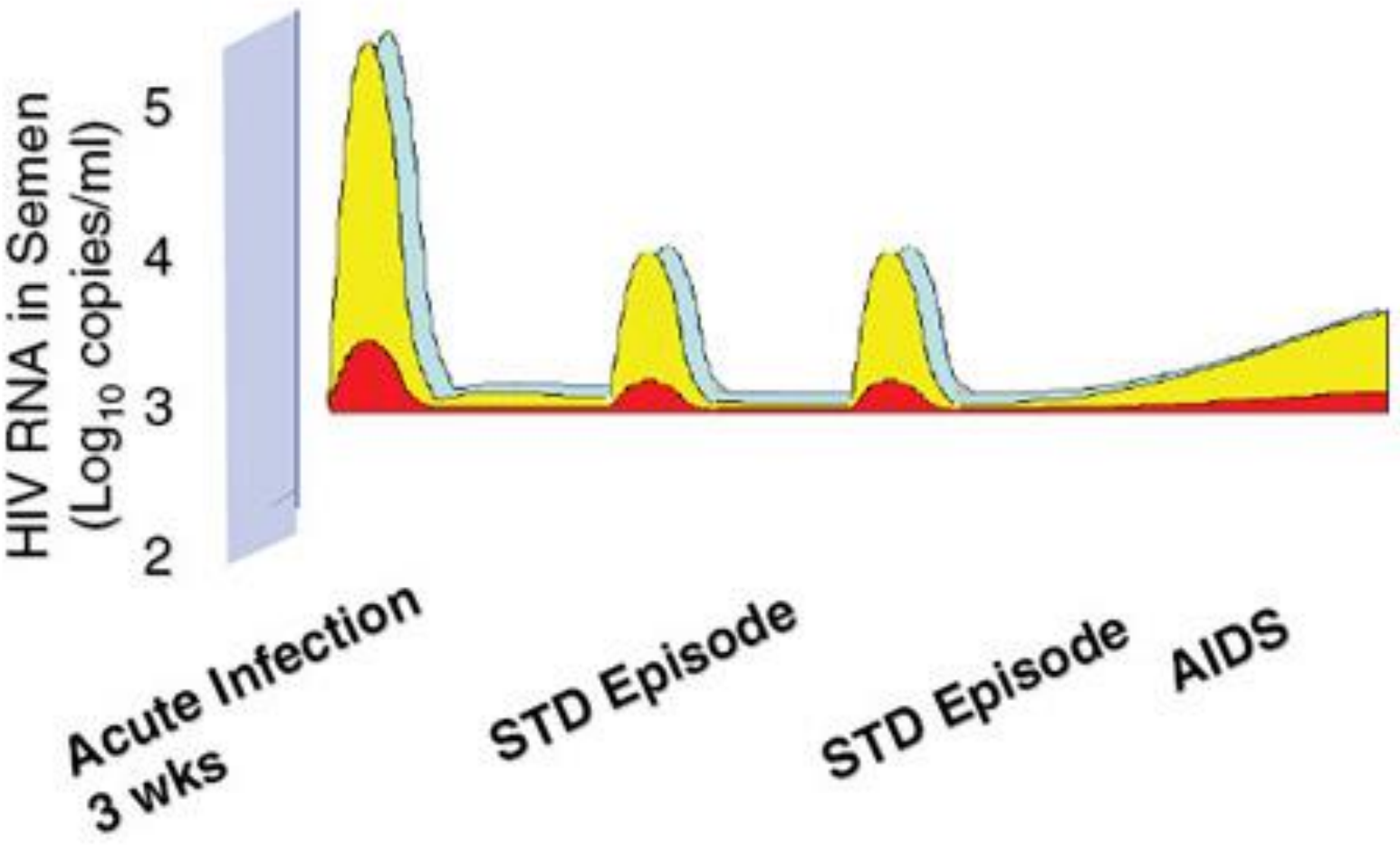
STDs and HIV Transmission

Secondary Prevention: STDs Increase the Risk of HIV Transmission

- STDs can increase the HIV viral load in the genital tract (genital lesion, female genital tract, semen)
- STDs may evoke a more infectious variant of HIV
- Co-transmission of STDs and HIV common

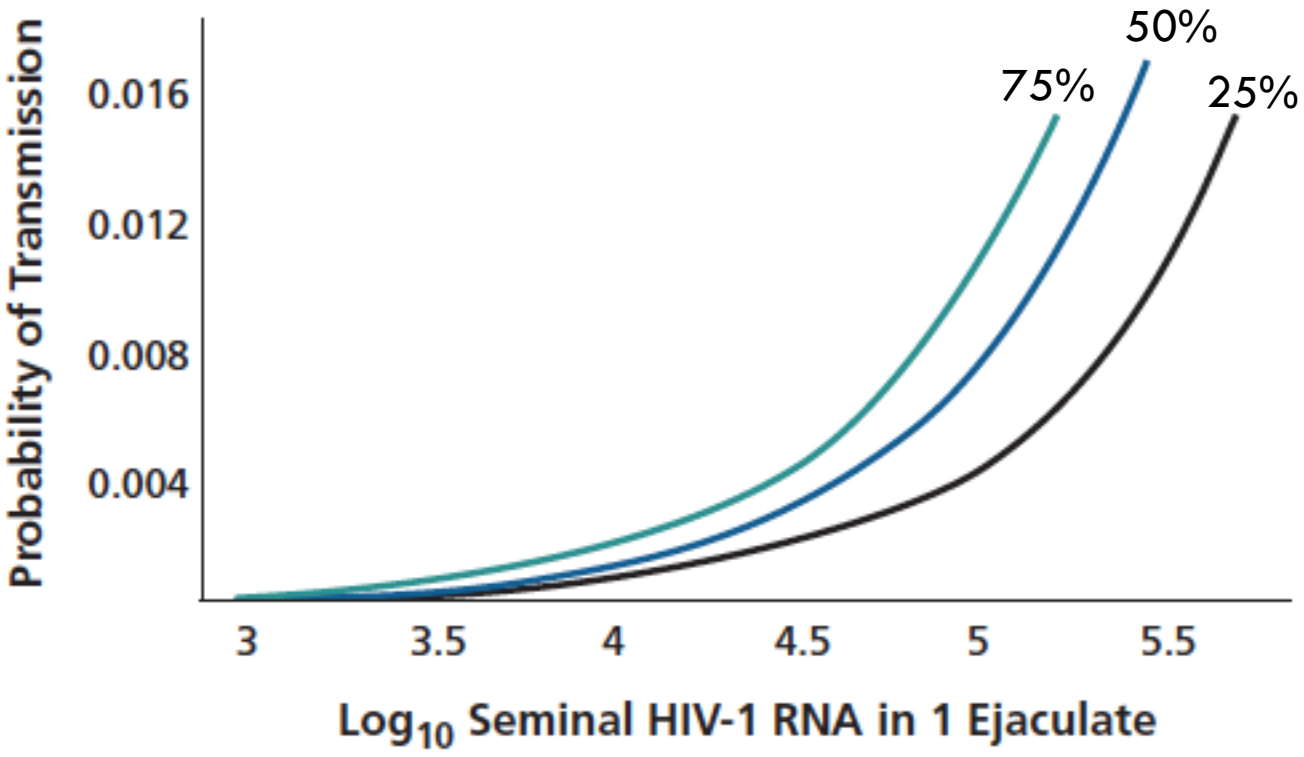
Cohen et al, Topics in HIV, 2004

HIV RNA in semen over time



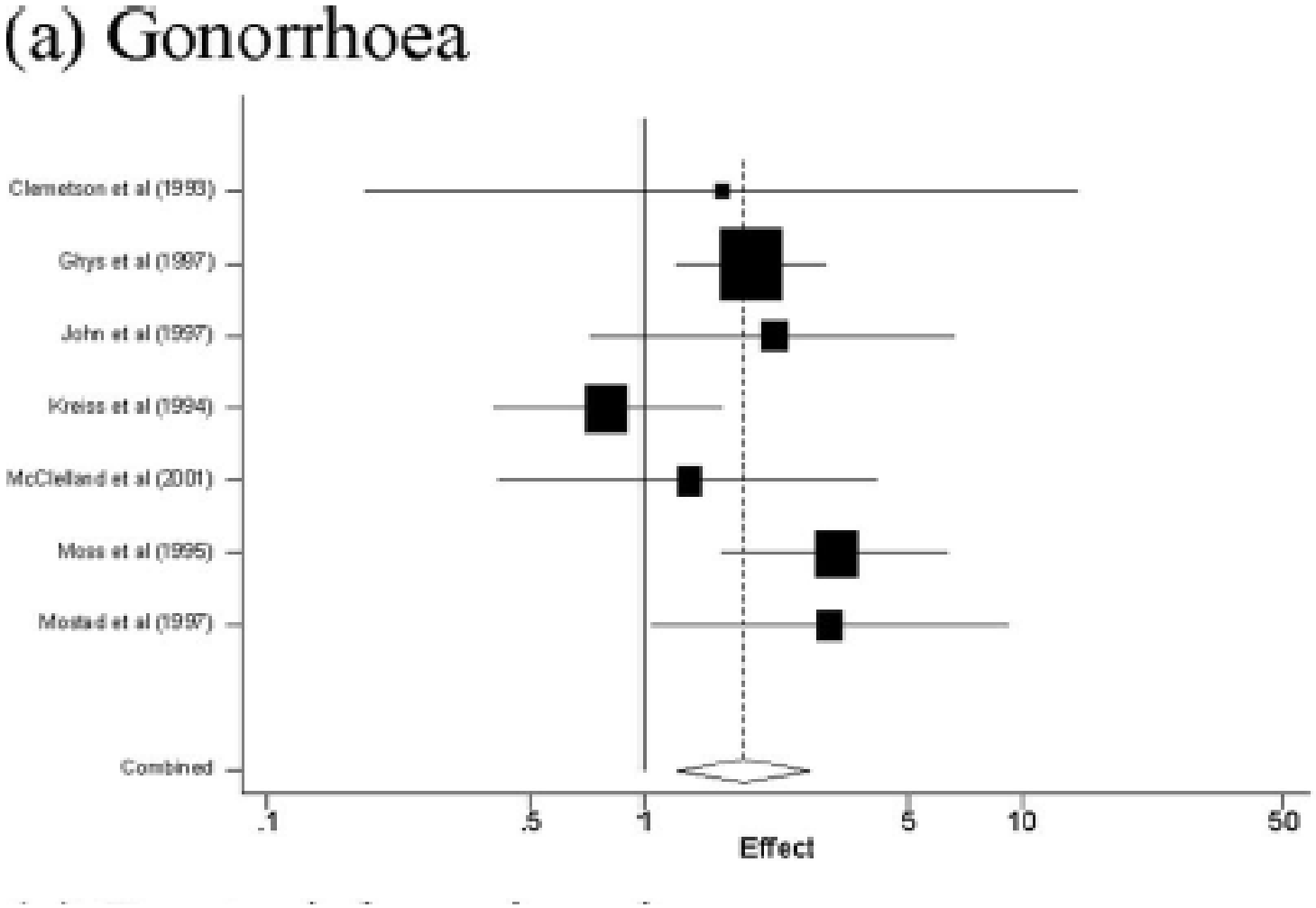
Cohen, et al. Sexually Transmitted Diseases, 2006

Increased seminal HIV VL and proportion cervical CCR5 cells present increases probability of male to female HIV transmission



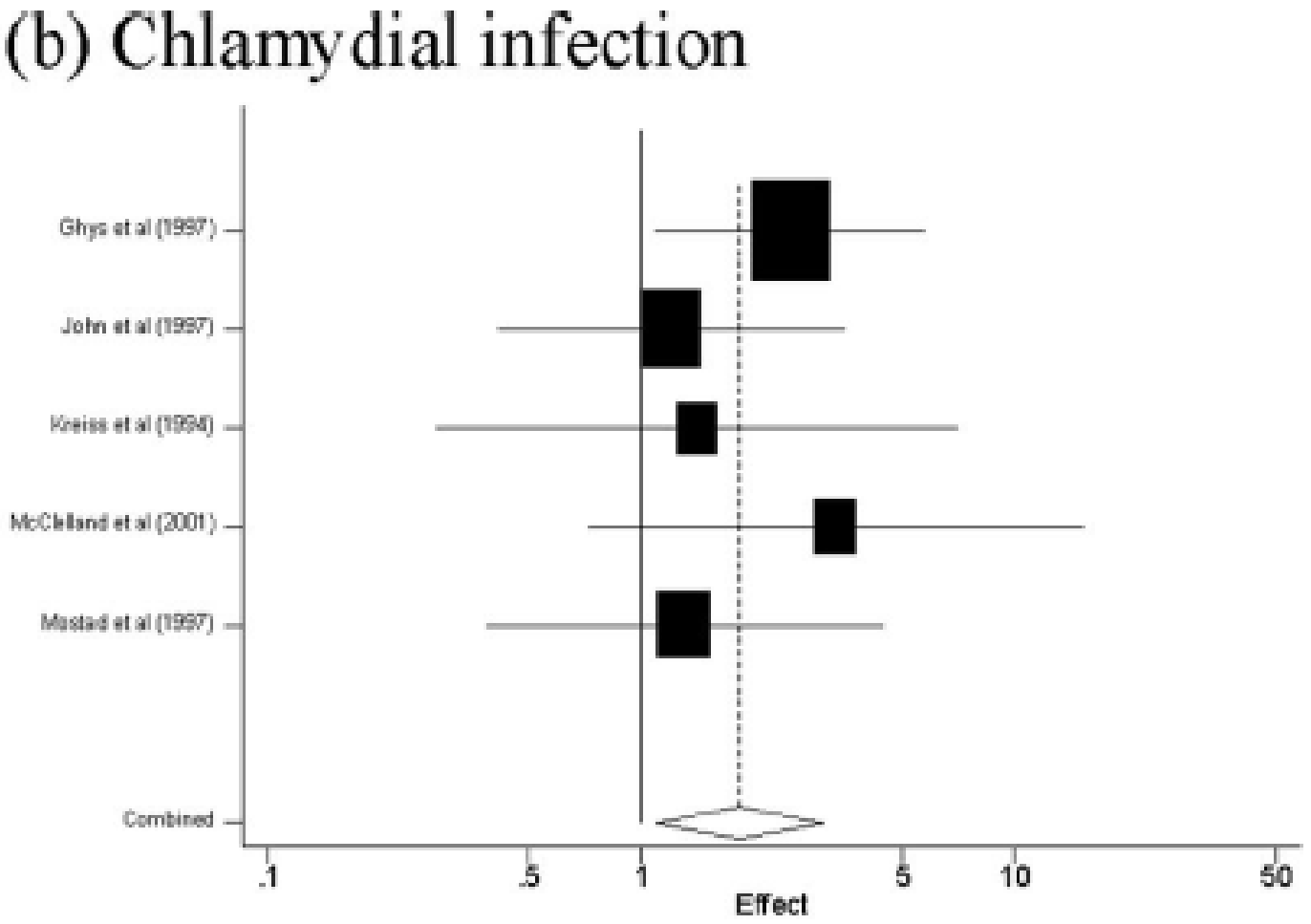
Chakraborty, AIDS 2001

Effect of Gonorrhea infection on HIV shedding in genital tract



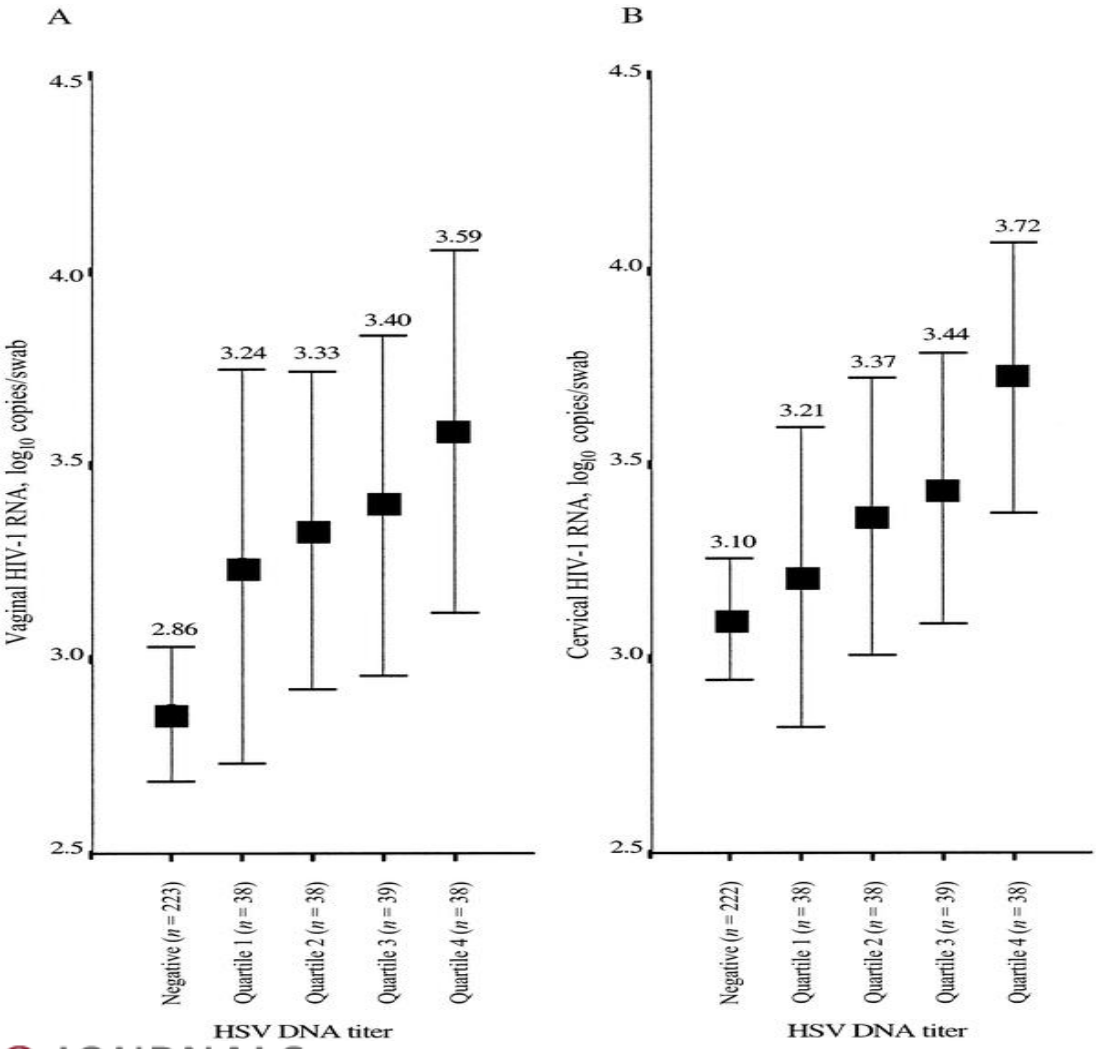
Johnson and Lewis, STD, 2008

Effect of Chlamydia infection on HIV shedding in genital tract



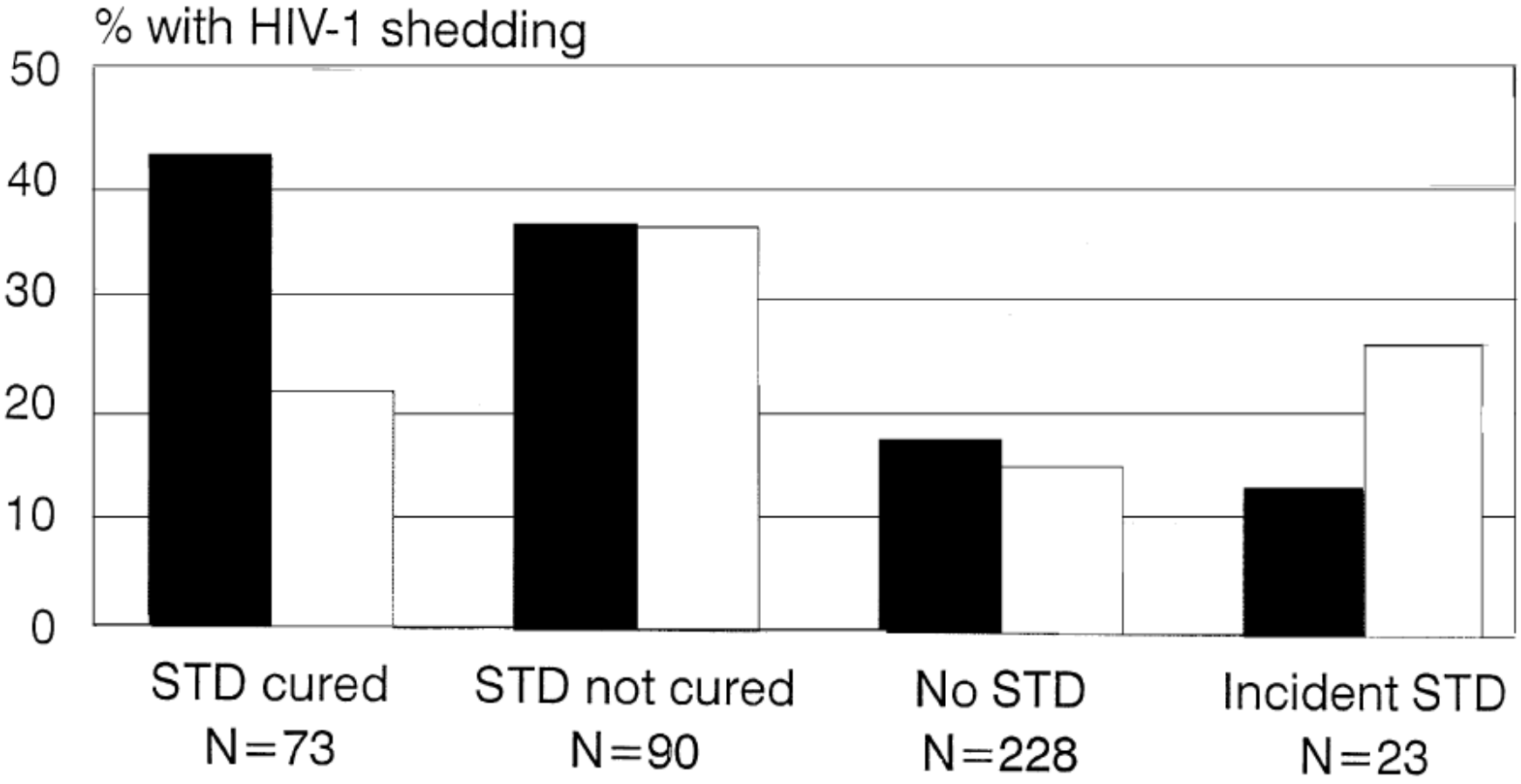
Johnson and Lewis, STD, 2008

Vaginal and cervical HIV RNA concentrations by increasing quartile of HSV DNA



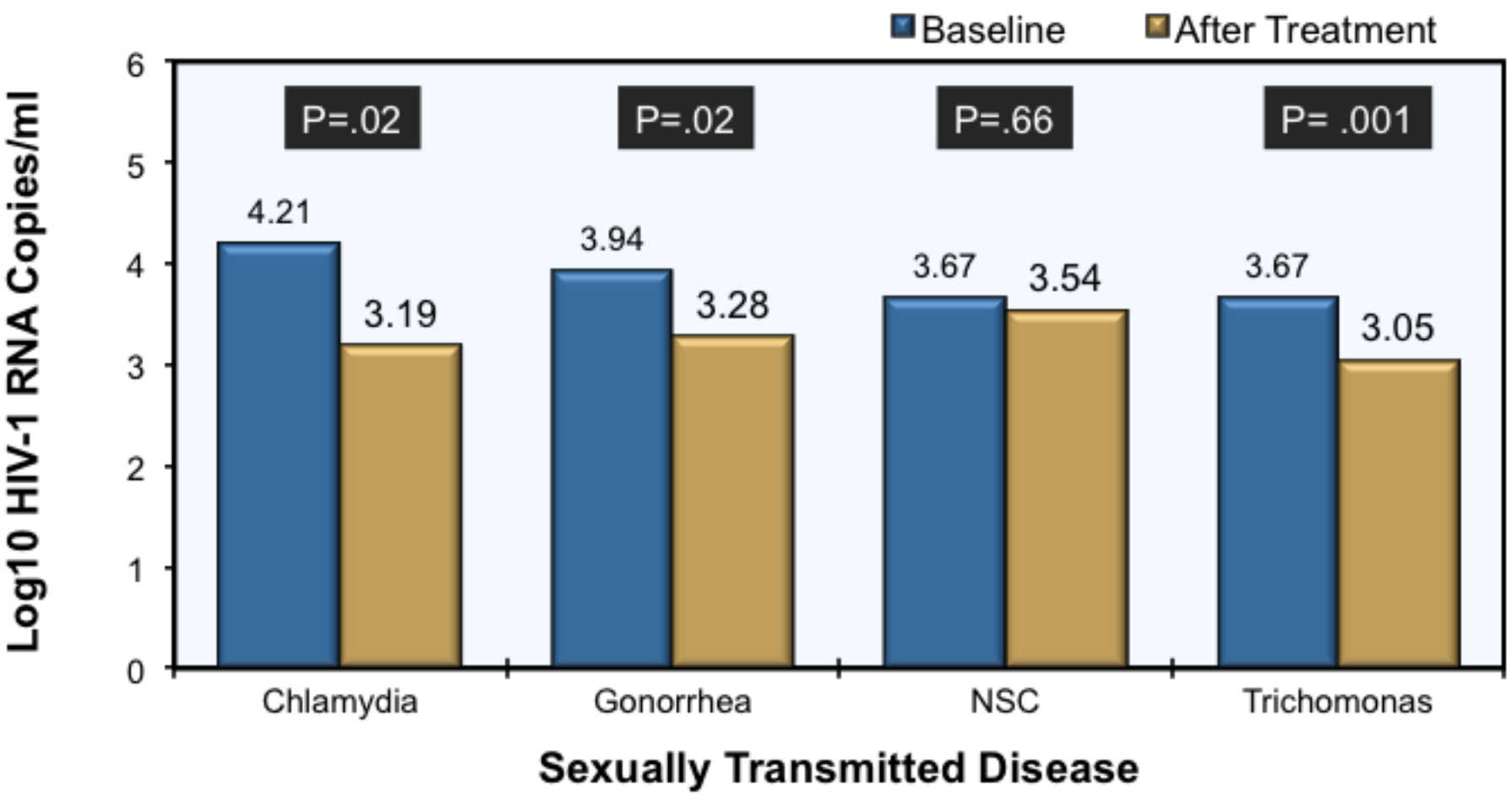
Baeten et al., Journal of Infectious Diseases, 2004

Treating STIs decreases HIV shedding



Ghys, AIDS, 1997

Decrease in HIV Viral Shedding after Treatment of Cervicitis and Vaginitis

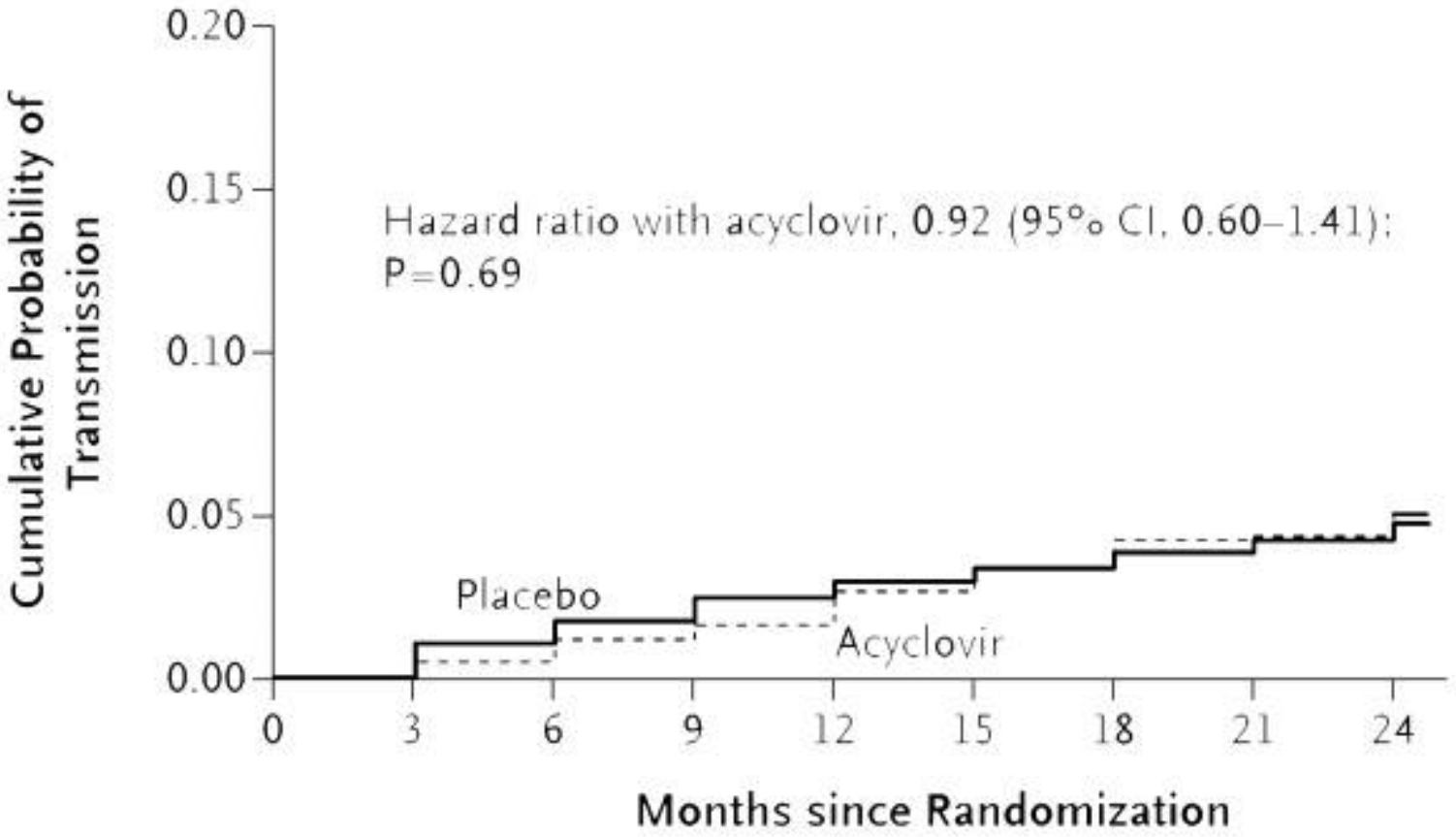


McClelland, AIDS, 2001; Wang, JID, 2001

Interventions of Population-based STD Treatment in Prevention of HIV

	Location	Baseline HIV prevalence	N	Design	Decrease in STDs?	Decrease in HIV incidence
Wawer 1999	Uganda	15%	10 community clusters 6602 intervention 6124 controls	RCT of azithro, cipro, metronidazole	yes	No
Grosskurth 1995	Tanzania	3.8-4.4%	12 community clusters 8845 subjects	RCT of STD clinic, meds	yes	Yes 1.9% v 1.2%
Kamali 2003	Uganda	4-20%	18 community Clusters 21000 subjects	RCT behavioral +/- STI clinic	Yes	No

Acyclovir and Transmission of HIV-1 from Persons Infected with HIV-1 and HSV-2



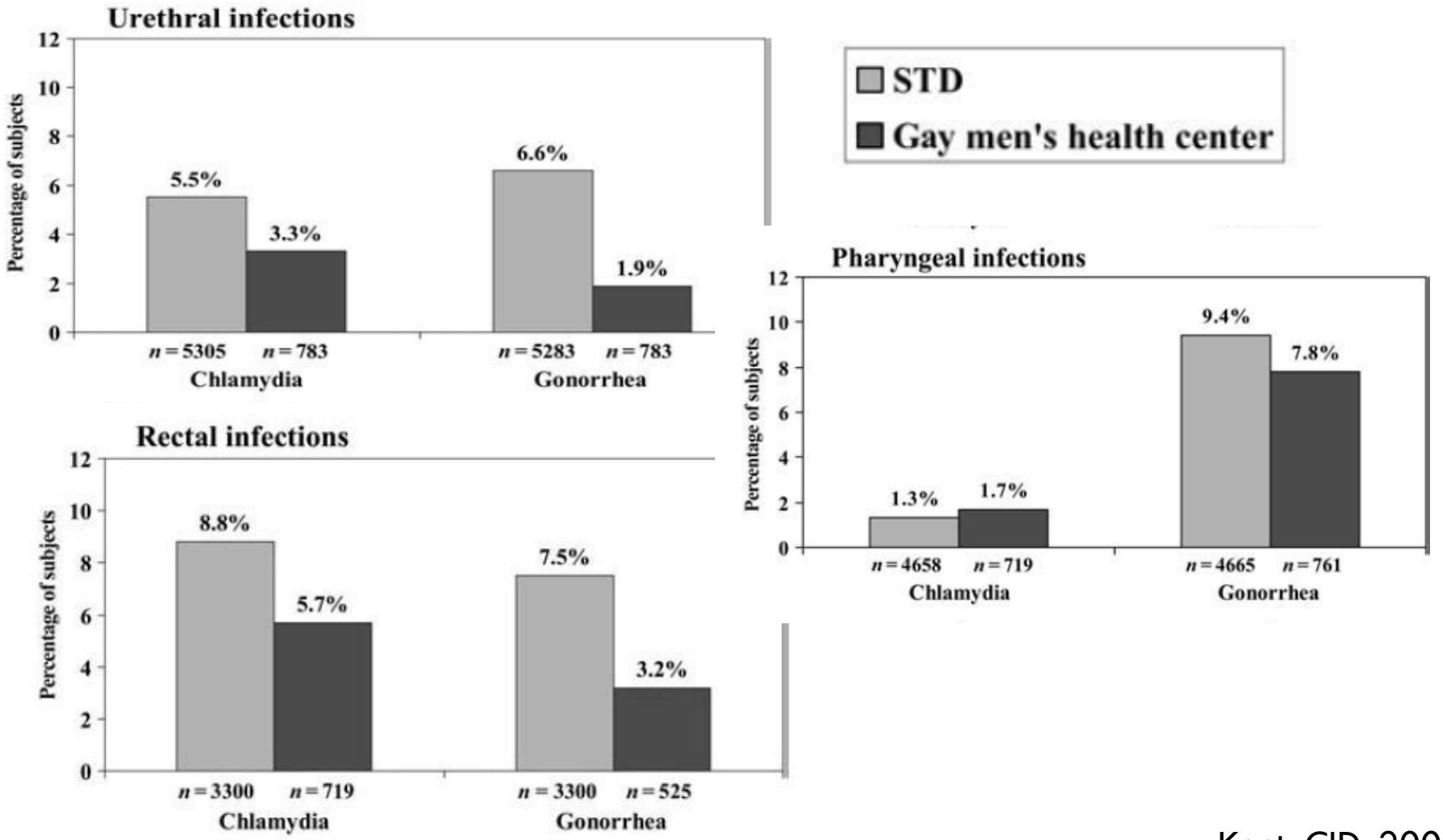
No. at Risk

Placebo	1654	1654	1610	1550	1434	1208	1021	760	570
Acyclovir	1640	1640	1577	1514	1389	1175	1000	761	565

Celum , NEJM, 2012

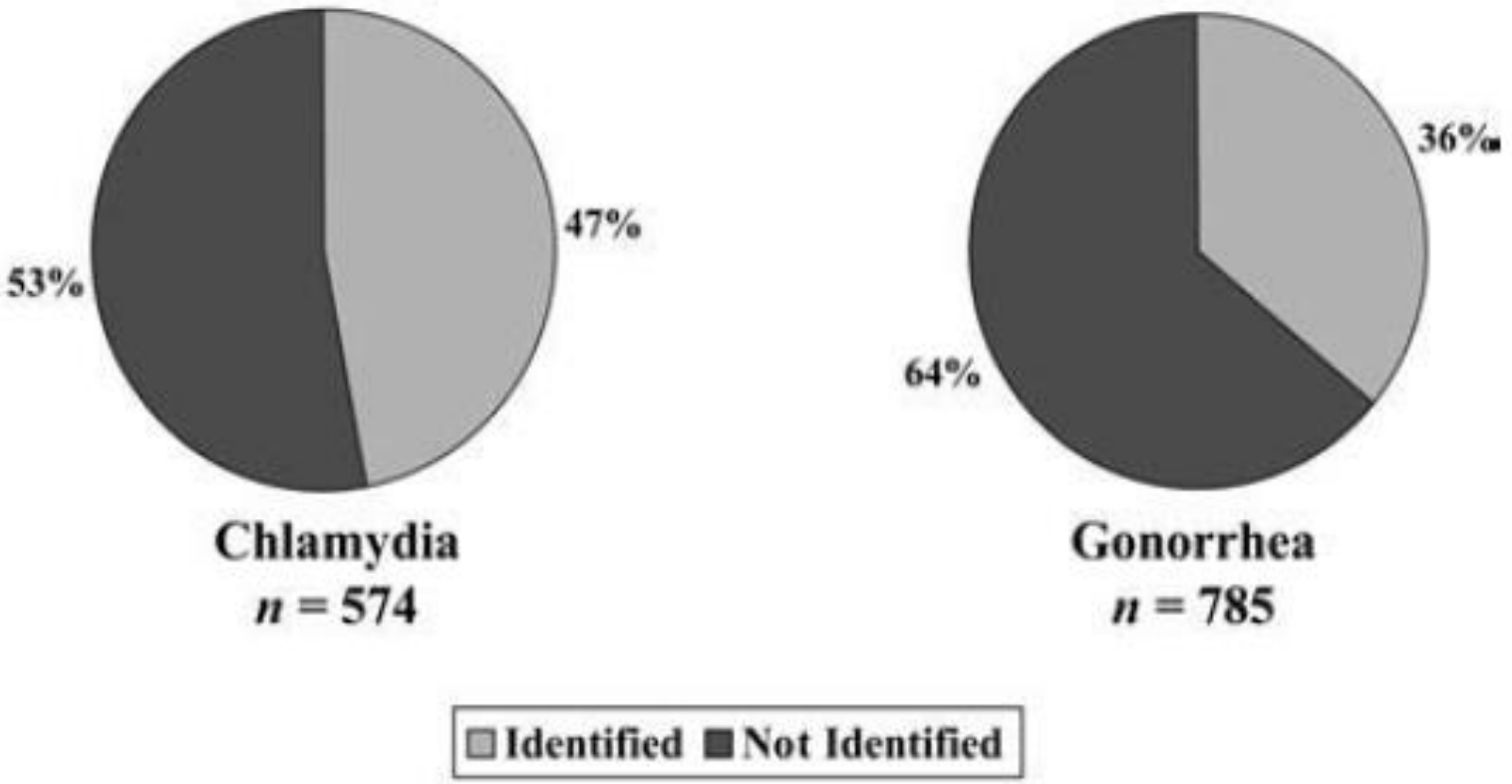
STD Prevalence and Incidence among HIV-infected Patients

Prevalence of STDs among MSM in SF



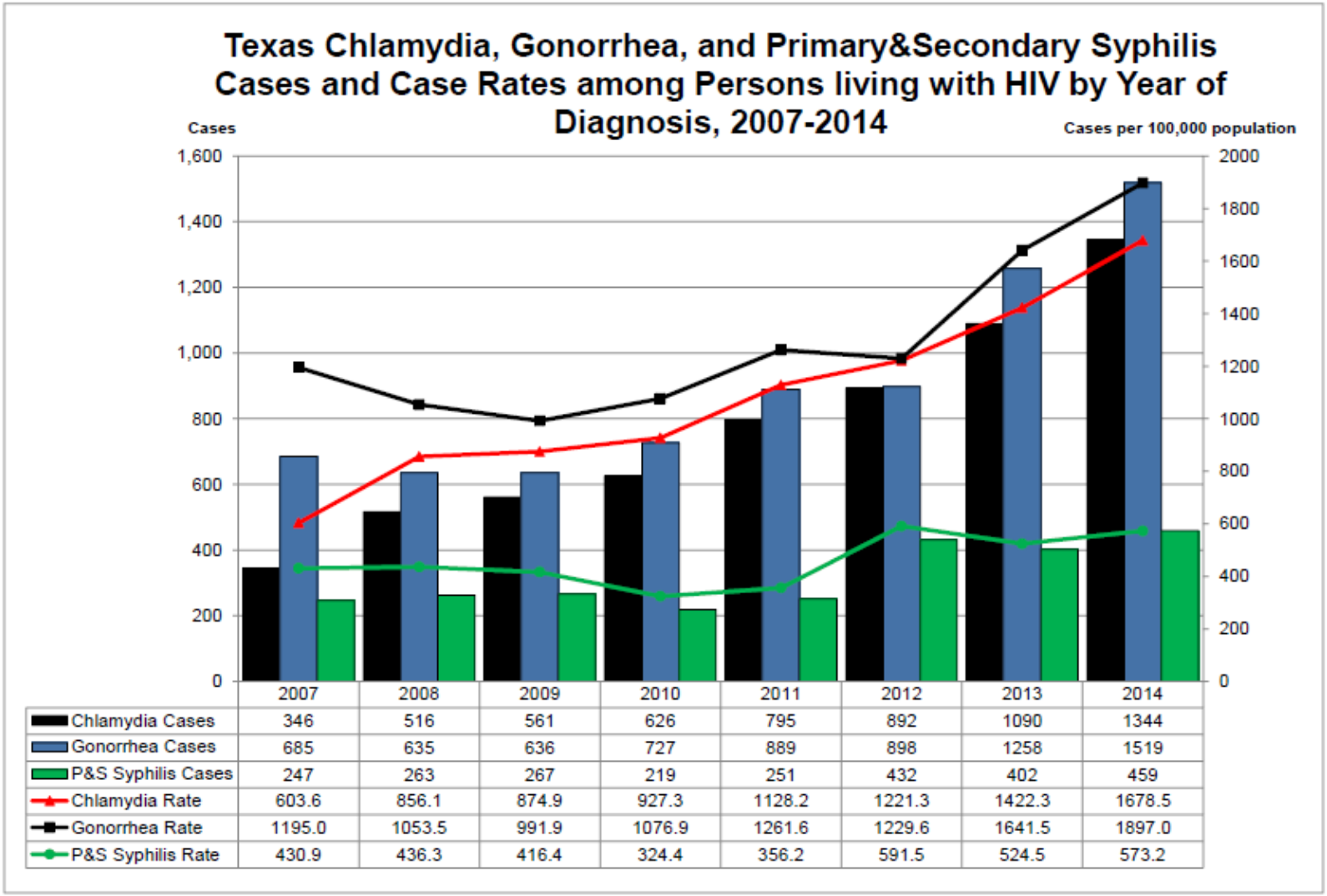
Kent, CID, 2005

Proportion of CT/GC Infections not identified if only urine/urethral screening performed



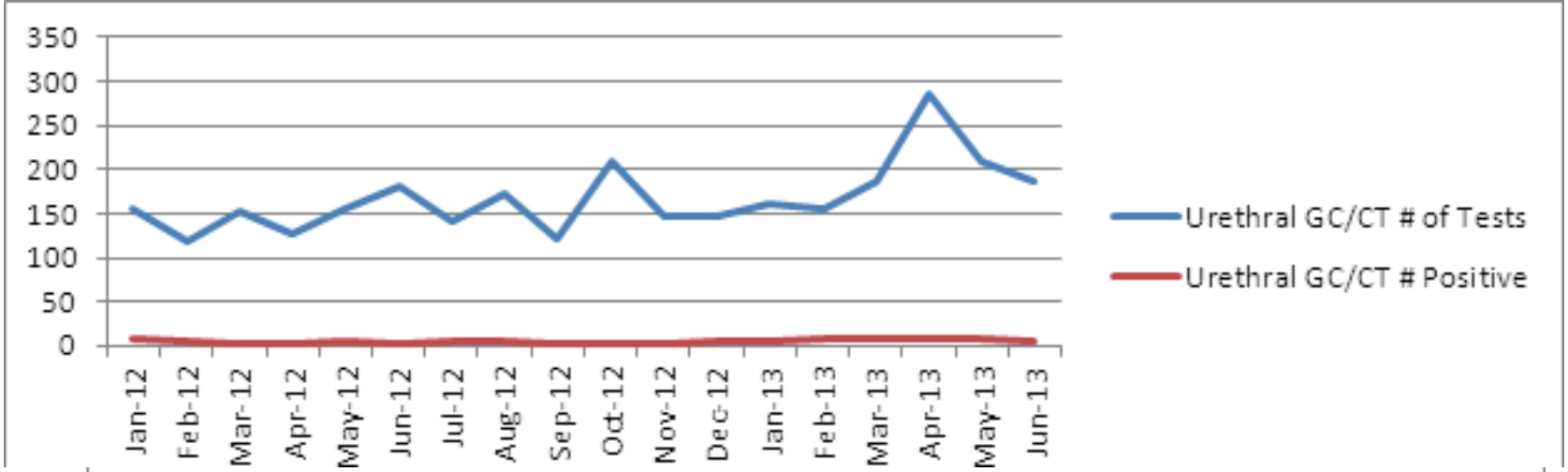
Kent, CID, 2005

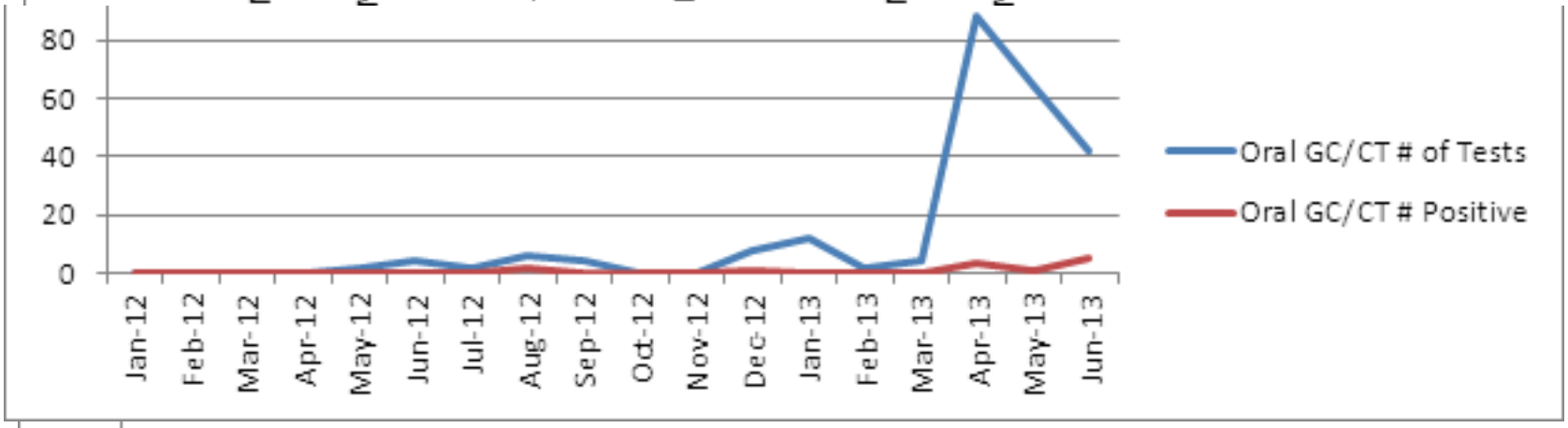
STDs among HIV+ in Texas

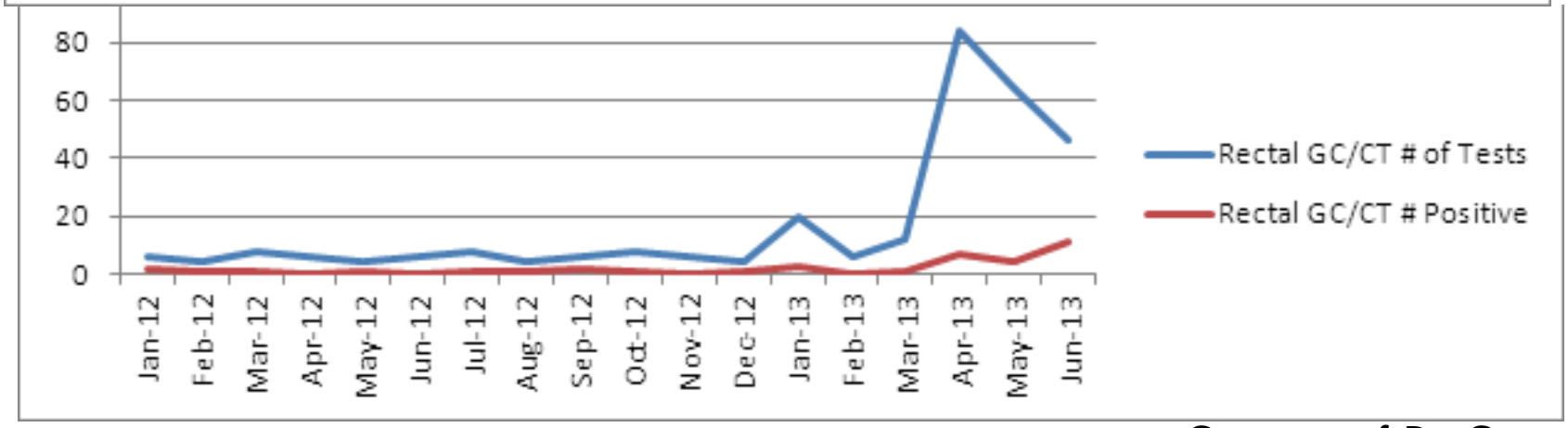


	2007	2008	2009	2010	2011	2012	2013	2014
Chlamydia Cases	346	516	561	626	795	892	1090	1344
Gonorrhea Cases	685	635	636	727	889	898	1258	1519
P&S Syphilis Cases	247	263	267	219	251	432	402	459
Chlamydia Rate	603.6	856.1	874.9	927.3	1128.2	1221.3	1422.3	1678.5
Gonorrhea Rate	1195.0	1053.5	991.9	1076.9	1261.6	1229.6	1641.5	1897.0
P&S Syphilis Rate	430.9	436.3	416.4	324.4	356.2	591.5	524.5	573.2

DSHS.state.tx.us







Courtesy of Dr. Gene Voskuhl

Screening and Counseling for STDs in HIV patients

IDSA HIV Primary Care Guidelines- STD screening in HIV patients

		Strength	Quality
Syphilis	All pt screened upon entering care and periodically after, based on risk	Strong	High
	LP should be performed for any pt with neuro or eye sx, regardless of prior treatment	Strong	High
	LP should be performed in pt with tx failure	Weak	Low
Trichomonas	Annual screening for all women	Strong	High
Chlamydia	Annual screening for all women ≤25, all sexually active MSM, all high risk women >25; initial visit	Strong	High
Gonorrhea	All sexually active MSM, high-risk women; initial visit	Strong	High
GC, CT, TV retesting	Retesting is indicated at 3 months for GC, CT, TV due to high re-infection rates	Strong	Moderate
Extra-genital testing	Testing for anorectal GC, CT with NAAT for those reporting receptive anal intercourse; for GC for those reporting receptive oral intercourse	--	--

IDSA HIV Primary Care Guidelines- STD screening in HIV patients, cont

		Strength	Quality
HPV	HIV+women should have a cervical Pap test upon initiation of care, at 6 months and annually thereafter if normal	Strong	Moderate
	Women with ASCUS, atypical glandular cells, LGSIL, HGSIL, or squamous CA on Pap testing should undergo colposcopy/directed biopsy, with further treatment as indicated	Strong	High
	MSM, women with a history of receptive anal intercourse or abnormal cervical Pap, and all HIV-infected persons with genital warts should have anal Pap tests	Weak	Moderate
	HPV vaccination is recommended for all females aged 9–26 years and all males aged 9–26	Strong	High
HBV	All pts screened with Hep Bs Ag, Hep Bs Ab, Hep Bc Ab	Strong	High
HCV*	All MSM at baseline and annually based on risk		

“High risk” definition

- Prior infection with STDs
- New or multiple sex partners
- Inconsistent condom use
- Commercial sex work
- Substance use
- Certain demographic groups
- Those living in communities with a high prevalence of disease

HRSA Core Measures for STDs

	Numerator	Denominator
Syphilis	Clients tested for Syphilis	>18 years old, sexually active Seen by medical provider
Chlamydia	Clients tested for Chlamydia	were either: a) newly enrolled in care; b) sexually active; or c) had an STI within the last 12 months, and had a medical visit with a provider at least once in the measurement year
Gonorrhea	Clients tested for Gonorrhea	Same as for Chlamydia
Cervical Cancer Screening	Clients with a Pap smear	>18 years old, sexually active Seen by medical provider
HBV screening	Clients with Hep B screening test since HIV dx	Dx of HIV with 2 medical visits at least 60 days apart within the past year

HIV Risk Counseling Documentation

- Documented counseling w/in past 12 months regarding:
  - Increased risk of transmitting HIV and safer sexual practices
  - Risk of acquiring syphilis and other STIs from unprotected sexual contact, including all sites of possible transmission, such as anus, cervix, vagina, urethra and oropharynx
  - Family planning method appropriate to patient's status
  - Preconception counseling as appropriate
  - Importance of disclosure to partners

Sexual History: The 5 Ps

- ***Partners***
  - Gender(s), Number (3 months, Lifetime)
- ***Prevention of pregnancy***
  - Contraception, EC
- ***Protection from STIs***
  - Condom use
- ***Practices***
  - Types of sex:
    - anal, vaginal, oral
- ***Past history of STIs***

Diagnosis and Treatment of STDs in HIV positive patients

Chlamydia trachomatis Diagnostics

- Women- urine or endocervix/vaginal swab
- Men- urine or urethral swab
- Rectal- rectal swab
- NAAT (nucleic acid amplification test)
  - Most sensitive
  - FDA cleared for endocervix, urethral swabs; urine
  - Not cleared for rectal
- Culture- very difficult
- DFA, EIA

Chlamydia trachomatis Treatment

- Azithromycin 1gm PO x1
- Doxycycline 100mg PO BID x 7 days

- Erythromycin base 500 mg PO QID x 7 days
- Erythromycin ethylsuccinate 800 mg PO QID x 7 d
- Levofloxacin 500mg PO QD x 7 days
- Ofloxacin 300mg BID x 7 days

Neisseria gonorrhoeae Diagnosis

- Gram stain of male urethral discharge- 99% specific, 95% sensitive if PMNs with intracellular gram-neg diplococci
  - Cannot definitively rule out infection
  - Not adequate for women, pharyngeal, or rectal specimens

Neisseria gonorrhoeae Diagnosis

- Culture
  - Fragile
  - Fastidious- require media with hemoglobin, NAD, etc
    - Chocolate agar/Modified Thayer Martin
- Other issues similar to Chlamydia
  - NAAT is best, but FDA cleared only for urogenital samples and urine

2015 Gonorrhea Treatment

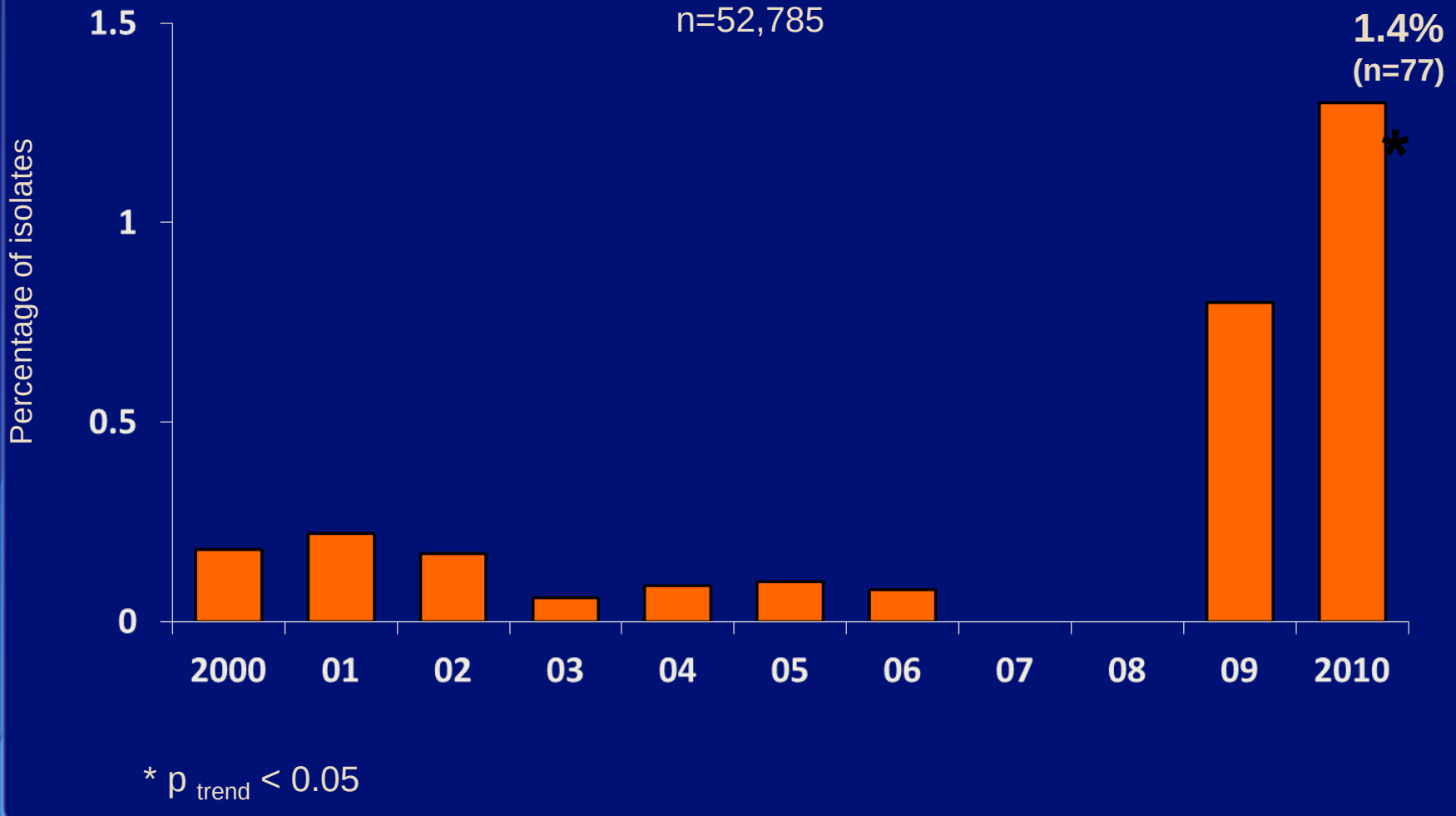
Uncomplicated Genital/Rectal Infections:

Ceftriaxone 250mg IM + **Azithromycin 1g po once**

IM much preferred if possible

- ✓ Can treat with Cefixime 400mg + Azithromycin if ceftriaxone not available
- ✓ Gemifloxacin 360mg (or Gentamicin 240mg IM) + azithromycin 2gm
- ✓ No longer an alternative: Azithromycin 2 gm po once; doxycycline-containing regimens
- ✓ Need to do test of cure if alternative regimen used (preferrably with culture)
- ✓ For all: Repeat test in 3 months to eval for re-infection

Proportion of isolates with elevated CEFIXIME MICs (≥ 0.25 µg/ml) Gonococcal Isolate Surveillance Project, US, 2000–2010



Vaginitis

- The big three
  - BV (caused by the replacement of the vaginal flora by an overgrowth of anaerobic bacteria including *Prevotella sp., Mobiluncus sp., G. vaginalis, Ureaplasma, Mycoplasma,* and numerous fastidious or uncultivated anaerobes)
  - Trichomoniasis (caused by T. vaginalis)
  - Candidiasis (usually caused by Candida albicans)
- History is insufficient to make diagnosis

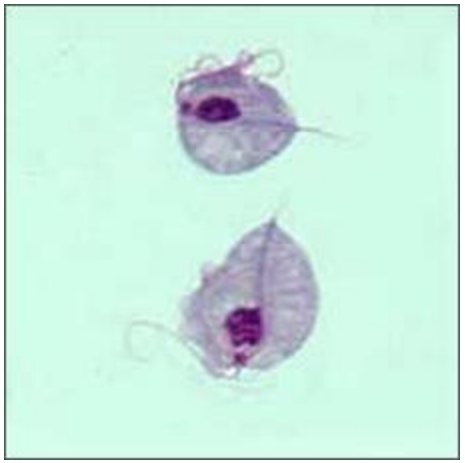
Vaginitis diagnostics

- pH of the vaginal secretions
  - an elevated pH (i.e., >4.5) is common with BV or trichomoniasis.
- KOH (sample in 1-2 drops of 0.9% saline, add 10% KOH)
  - Amine odor => BV or trichomoniasis
- Wet prep
  - motile *T. vaginalis*
  - Clue cells (i.e., epithelial cells with borders obscured by small bacteria)

Vaginitis management

A 38 yo woman with HIV comes in for her annual well woman exam. You perform a pap smear, testing for gonorrhea and chlamydia, and also perform a wet mount. This is what you see. She reports no vaginal symptoms but states that she has had trichomonas infection in the past. What do you do next?

A. Don't treat, she has no symptoms
B. Treat with Metronidazole gel
C. Give her metronidazole 2 gm po x 1
D. Treat her with metronidazole 500mg po bid x 1 week



Trichomonas Treatment and Follow up

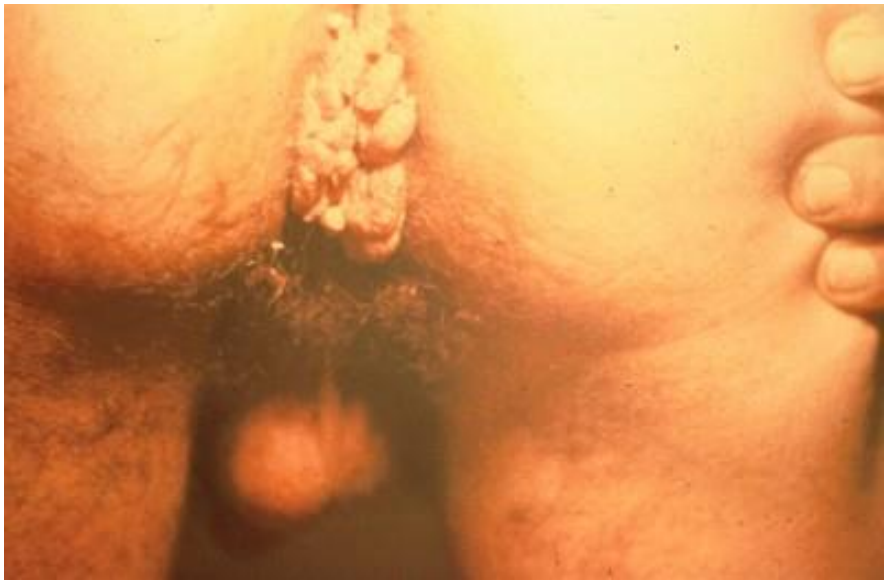
- Treatment: metronidazole 2 gm po once
- Because of the high rate of reinfection among patients with trichomoniasis
  - Rescreening at 3 months following initial infection can be considered for sexually active women with trichomoniasis;
  - No data support rescreening in men
- Treatment failure (and not reinfection)
  - Low-level metronidazole resistance in 2%–5% of cases of vaginal trichomoniasis
    - *most of these organisms respond to tinidazole or higher doses of metronidazole.*
    - *Tinidazole has a longer serum half-life and reaches higher levels in genitourinary tissues than metronidazole.*
  - If failure with metronidazole 2-g single dose → metronidazole 500 mg orally twice daily for 7 days.
    - IF this fails → treat with tinidazole or metronidazole at 2 g orally for 5 days

Condyloma

One of your HIV patients presents for a routine visit and states that he has noticed growths around his anal area. His risk factor for HIV is sex with men.

Which of the following statements is true:

A. This patient is at low risk for developing anal cancer
B. Anal warts are predominantly caused by high risk HPV subtypes (16 or 18)
C. HIV patients respond equally well to treatment for genital warts as HIV negative patients
D. This patient should be managed in conjunction with proctology or colorectal surgeon



Human Papilloma Virus

- High-risk HPV types (16 and 18): cervical cancer
- Low-risk HPV types (6 and 11): genital warts.
- **HPV tests** are available for women aged >30 years undergoing cervical cancer screening (not for men, for women <30 years of age, or as a general test for STDs) In women 15–25 years of age, ~80% of HPV infections are transient.
- **Treatment** is directed to the macroscopic (i.e., genital warts) or pathologic (i.e, precancerous) lesions caused by infection. Subclinical genital HPV infection typically clears spontaneously
- **Prevention**, two HPV vaccines are licensed in the United States:
  - Bivalent: (Cervarix) containing HPV types 16 and 18
  - Quadrivalent vaccine (Gardasil) vaccine containing HPV types 6, 11, 16,18.
  - Can be given ages 9-26, in girls and boys, typically ages 11-12, prior to onset of sexual activity

HPV and HIV

- HIV patients more likely to develop genital warts
- May have larger or more numerous warts
- May not respond as well to therapy
- Squamous cell CA can arise in or resemble anal condyloma, so may need referral for biopsy
- Some centers routinely screen HIV+ patients for anal cancers using pap smears

Syphilis and HIV

- Primary:
  - 70% have more than one ulcer
  - Deeper and larger ulcerations
- Secondary:
  - May see primary and secondary syphilis at the same time in HIV + patients
- Neurosyphilis
  - Not neccesarily a late manifestation, can occur early on in disease
  - Unclear if represents higher treponemal invasion due to immunocompromise versus higher rates of baseline CSF abnormalities
  - Male gender, CD4 <350, RPR >1:32 associated with neurosyphilis in HIV

When to perform LP in HIV patient with syphilis

- Neurologic symtpoms
  - meningitis, meningoencephalitis, deafness, weakness, numbness, cranial nerve involvement, cognitive issues
- Eye involvement
  - optic neuritis, uveitis

Treatment of syphilis

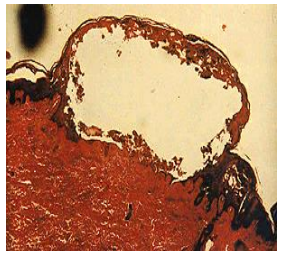
Condition	Treatment	Comments
Primary, Secondary, early latent	Benzathine Penicillin G	2.4 million units IM x 1
Late latent, unknown duration, tertiary (non-neurosyphilis)	Benzathine Penicillin G	2.4 million units IM weekly x 3
Neurosyphilis	Aqueous crystalline Penicillin G	3-4 million untis IV q 4h or continuous x 10-14 d.
Neurosyphilis alternative	Benzathine Penicillin G + probenecid	2.4 million units IM daily + 500mg qid x 10-14d
Pregnancy	Benzathine Penicillin G	Must be desensitized if allergic
HIV	Benzathine Penicillin G	As above
PCN- allergy	Doxycycline/tetracycline (Azithromycin*; Ceftriaxone)	Only in non-pregnant patients; doxy/tetra only alternative for late latent

Follow-up after treatment

- Everyone with syphilis should be tested for HIV (repeat in 3 months)
- Exam and serology 6, 12 months
- HIV infected: Exam and serology at 3, 6, 9, 12, 24 months
- In HIV infected and those with repeat infections, titer may be slower to drop
- If persistent symptoms, or persistent titer elevation :
  - Retest for HIV
  - Consider LP
  - Re-treat (Benz Pen G 2.4 million units weekly IM x 3)
- Neurosyphilis: if initial CSF pleocytosis, repeat LP at 6 months

Genital Herpes

- Indications for type-specific HSV serology:
  1. Recurrent or atypical symptoms with negative HSV culture/PCR of lesion(s).
  2. Partner with genital herpes.
  3. Anyone with HIV infection.
  4. Consider in clients with multiple sexual partners
  5. Men who have sex with men at risk for HIV acquisition.



- *Not* indicated for routine screening of the general population or routine screening of pregnant women.

Denver PREVENTION TRAINING CENTER

Herpes Simplex Virus

- Ulcer(s) today -> culture the lesion.

  Virus culture is still the preferred method for diagnosing HSV

- Sensitivity declines as lesions heal
  - Vesicles = 90%
  - Ulcers = 70%
  - Crusted lesions = 30%

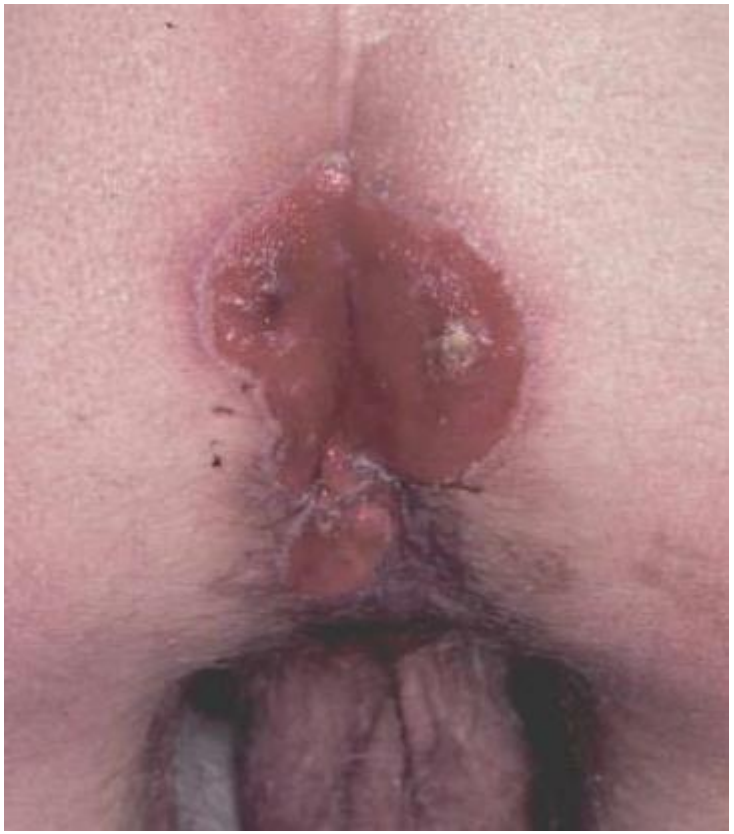
  If primary episode, HSV serology not yet positive.

Skin ulcers in HIV patient

A 34 yo HIV patient with CD4 <100 presents with painful ulcers on buttocks.

What would be the next appropriate step in management:

A. Perform a viral culture or PCR
B. Obtain HSV IgM serology
C. Tzanck preparation



You perform the appropriate test on this patient and determine that he has HSV. He is treated with a prolonged course of Acyclovir but does not improve and in fact, his ulcers are worse. You suspect resistant HSV and switch treatment to the following:

A. Valacyclovir
B. Famciclovir
C. Foscarnet
D. IV acyclovir
E. Topical acyclovir

LGV

- Caused by Chlamydia trachomatis, serovars L1, L2, L3
- Previously rare, now have seen outbreaks in developed world among MSM in urban areas
- Most of these are presenting with proctitis (not ulcers) and are among HIV+ (76%)
- Primary infection: painless ulcer
- Secondary infection (2-6 weeks later):
  - LAN (groove sign);
  - Proctitis (discharge, fever, tenesmus, mimics IBD)

  Dx: send swabs to local or state laboratory (for NAAT testing), serology not validated but may be suggestive

  Tx: Doxycycline for 21 days

Conclusions

- STDs Increase HIV Acquisition and HIV Transmission, therefore the diagnosis, treatment and prevention of STDs are key components of primary and secondary HIV prevention
- There is a high incidence and prevalence of STDs among HIV infected patients, especially MSM
- A significant proportion of STDs are likely missed due to asymptomatic extra-genital infections
- IDSA and HRSA, among others, have set forth guidelines/core measures for STD screening in HIV+ patients

Conclusions

- The clinical presentation of STDs in HIV patients may be more severe, such as larger lesions which take longer to heal (HSV), early manifestation of advanced clinical finding (syphilis), multiple, large condyloma (HPV)
- The treatment may vary for HIV infected patients (e.g. longer metronidazole for trichomonas, Foscarnet for resistant HSV) with more aggressive surveillance of recurrence (HPV, syphilis)
- We likely under-diagnose STDs in our HIV patients and miss opportunities for risk counseling