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

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 al., 2003
## Types and Characteristics of STDs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aetiological agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic infections without mucosal disease</td>
<td>HIV, hepatitis B, cytomegalovirus</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td><em>Haemophilus ducreyi</em>, herpes simplex virus 1 and 2, <em>Treponema pallidum</em></td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td><em>Neisseria gonorrhoeae</em>, <em>Chlamydia trachomatis</em>, <em>Trichomonas vaginalis</em></td>
</tr>
<tr>
<td>Changes in epithelial cells</td>
<td>Human papillomavirus</td>
</tr>
</tbody>
</table>
Pooled Risk Effect of Non-Ulcerative STDs on Susceptibility to HIV

![Graph showing the pooled risk effect of various sexually transmitted diseases on susceptibility to HIV.](Rottingen, STD, 2001)
Pooled Risk Effect of Genital Ulcer Diseases on Susceptibility to HIV

- HSV: 2.7
- Syphilis: 2.5
- Chancroid: 2.1
- GUD: 2.7

Rottingen, STD, 2001
2,499 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
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.
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
Treating STIs decreases HIV shedding

% with HIV-1 shedding

- STD cured N=73
- STD not cured N=90
- No STD N=228
- Incident STD N=23

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

<table>
<thead>
<tr>
<th>Location</th>
<th>Baseline HIV prevalence</th>
<th>N</th>
<th>Design</th>
<th>Decrease in STDs?</th>
<th>Decrease in HIV incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wawer 1999</td>
<td>Uganda</td>
<td>15%</td>
<td>10 community clusters 6602 intervention 6124 controls</td>
<td>RCT of azithro, cipro, metronidazole</td>
<td>yes</td>
</tr>
<tr>
<td>Grosskurth 1995</td>
<td>Tanzania</td>
<td>3.8-4.4%</td>
<td>12 community clusters 8845 subjects</td>
<td>RCT of STD clinic, meds</td>
<td>yes</td>
</tr>
<tr>
<td>Kamali 2003</td>
<td>Uganda</td>
<td>4-20%</td>
<td>18 community Clusters 21000 subjects</td>
<td>RCT behavioral +/- STI clinic</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Acyclovir and Transmission of HIV-1 from Persons Infected with HIV-1 and HSV-2

Hazard ratio with acyclovir, 0.92 (95% CI, 0.60–1.41); P = 0.69

Cumulative Probability of Transmission

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

Urethral infections

<table>
<thead>
<tr>
<th></th>
<th>STD</th>
<th>Gay men's health center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia</td>
<td>5.5%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>6.6%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Rectal infections

<table>
<thead>
<tr>
<th></th>
<th>STD</th>
<th>Gay men's health center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia</td>
<td>8.8%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>7.5%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

Pharyngeal infections

<table>
<thead>
<tr>
<th></th>
<th>STD</th>
<th>Gay men's health center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia</td>
<td>1.3%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>9.4%</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

Kent, CID, 2005
Proportion of CT/GC Infections not identified if only urine/urethral screening performed

Chlamydia
$n = 574$

- Identified: 53%
- Not Identified: 47%

Gonorrhea
$n = 785$

- Identified: 64%
- Not Identified: 36%

Kent, CID, 2005
STDs among HIV+ in Texas

Texas Chlamydia, Gonorrhea, and Primary&Secondary Syphilis Cases and Case Rates among Persons living with HIV by Year of Diagnosis, 2007-2014
Screening and Counseling for STDs in HIV patients
# IDSA HIV Primary Care Guidelines - STD screening in HIV patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Screening Recommendations</th>
<th>Strength</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>All pt screened upon entering care and periodically after, based on risk</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>LP should be performed for any pt with neuro or eye sx, regardless of prior treatment</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>LP should be performed in pt with tx failure</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>Annual screening for all women</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Annual screening for all women ≤25, all sexually active MSM, all high risk women &gt;25; initial visit</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>All sexually active MSM, high-risk women; initial visit</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>GC, CT, TV retesting</td>
<td>Retesting is indicated at 3 months for GC, CT, TV due to high re-infection rates</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Extra-genital testing</td>
<td>Testing for anorectal GC, CT with NAAT for those reporting receptive anal intercourse; for GC for those reporting receptive oral intercourse</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Condition</td>
<td>TestRecommendation</td>
<td>Strength</td>
<td>Quality</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>HPV</td>
<td>HIV+women should have a cervical Pap test upon initiation of care, at 6 months and annually thereafter if normal</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Women with ASCUS, atypical glandular cells, LGSIL, HGSIL, or squamous CA on Pap testing should undergo colposcopy/directed biopsy, with further treatment as indicated</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>MSM</td>
<td>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</td>
<td>Weak</td>
<td>Moderate</td>
</tr>
<tr>
<td>HCV</td>
<td>HPV vaccination is recommended for all females aged 9–26 years and all males aged 9–26</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>HBV</td>
<td>All pts screened with Hep Bs Ag, Hep Bs Ab, Hep Bc Ab</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>HCV*</td>
<td>All MSM at baseline and annually based on risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
"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

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

www.stdhivtraining.net
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 days
- 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:**

- 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 (preferably with culture)
  - For all: Repeat test in 3 months to eval for re-infection

**Ceftriaxone 250mg IM** + **Azithromycin 1g po once**
Proportion of isolates with elevated CEFIXIME MICs (≥ 0.25 μg/ml)
Gonococcal Isolate Surveillance Project, US, 2000–2010

Percentage of isolates

n=52,785

1.4% (n=77)

* p trend < 0.05
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)
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
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 necessarily 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 symptoms
  - meningitis, meningoencephalitis, deafness, weakness, numbness, cranial nerve involvement, cognitive issues

- Eye involvement
  - optic neuritis, uveitis
# Treatment of syphilis

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