Sexually Transmitted Infections:
Hot topics & updates from the 2015
CDC STD Treatment Guidelines

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and Sexual Health Update
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Disclosures

• Christine Johnston does not have relationships with a commercial interest related to the content of this educational activity.

• Dedicated to increasing the knowledge and skills of healthcare providers in the area of sexual health
• Education and training programs are specifically designed for physicians, nurses, physician assistants, nurse practitioners and laboratorians
• Training content and priorities based on the most current CDC STD Treatment Guidelines, STD epidemiological trends, and scientific advancements
Objectives

1. Review epidemiology of STI in Minnesota
2. Discuss STI screening in at-risk populations
3. Review 2015 CDC STD Treatment Guidelines
4. Describe emerging STIs, including Zika virus

Why Diagnose and Treat STDs?

- >19 million STDs in U.S. annually
- Health consequences of untreated STDs
  - Women’s reproductive health
    - Untreated chlamydia or gonorrhea may lead to pelvic inflammatory disease (PID) & other consequences
    - Leading infectious cause of infertility in the U.S.
    - Trichomoniasis, BV associated with preterm delivery, low birth weight
  - Infant mortality/morbidity
    - Neonatal herpes and congenital syphilis
  - HIV transmission: identifying people who would benefit from HIV pre-exposure prophylaxis (PrEP)
- Health care cost
  - $15.6 billion
At Greatest Risk

- **Youth**
  - Nearly 50% of STDs estimated to occur in 15-24 year olds
- **Racial/ethnic minorities**
  - STDs among highest of all racial/ethnic health disparities
  - African-Americans
    - Chlamydia: 5.8 times the rate among whites
    - GC: 12.4 times
    - Early syphilis: 5.6 times
- **Men Who Have Sex with Men (MSM)**
  - Accounted for 75% of syphilis cases in 2013
  - High rates of HIV co-infection

Source: Minnesota Department of Health 2015 STD Surveillance Data Release

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**STDs in Minnesota**

Rate per 100,000 by Year of Diagnosis, 2005-2015

- Chlamydia
- Gonorrhea
- P&S Syphilis

Source: Minnesota Department of Health 2015 STD Surveillance Data Release

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**Chlamydia Infections by Residence at Diagnosis Minnesota, 2015**

Total Number of Cases = 21,238

Source: Minnesota Department of Health 2015 STD Surveillance Data Release
Sexually transmitted infections:
  - Continues to be a dynamic and rapidly changing field
  - Diagnostic and treatment issues
    - Extragenital screening
    - Expedited Partner Therapy
    - NGU/Mycoplasma genitalium
    - Trichomonas
  - Old/new issues:
    - GC resistance
    - Syphilis: Ocular, congenital
  - Prevention issues:
    - PrEP
    - HPV
  - Emerging infections:
    - Hep C
    - Zika

STD Screening: Requires asking

“Whoa—way too much information.”

Chlamydia & Gonorrhea: Diagnostic Testing

- Nucleic acid amplification tests (NAAT) recommended for men & women
- Optimal specimen: first-catch urine in men and vaginal swabs in women
- NAAT optimal for rectal and pharyngeal testing; not FDA approved but commercially available & validation protocols available
- Cannot perform drug resistance testing on NAAT (need culture if concern)
STI Screening in Women

- Sexually active adolescents <25 years of age
  - Annual chlamydia and gonorrhea screening
  - Other STIs based on risk

- Women ≥25 years of age
  - STI screening and testing based on risk

STI Screening in Pregnant women

- Chlamydia & gonorrhea (<25 years of age or at-risk)
  - Retest CT in 3rd trimester if <25 or high risk (both GC/CT)
- HIV
- Syphilis serology
  - First prenatal visit
  - 28 weeks gestation (at minimum between 28-36 weeks)
  - Delivery
- Hepatitis B sAg
- Hepatitis C (if high risk or fulfills other criteria)

Recommendations for STI Screening in MSM

- At least annually (more often if multiple/anonymous partners, meth use, recent STI, unprotected anal intercourse)
  - HIV
  - Syphilis
  - GC/CT of all sites at risk
    - (urethral, rectal, pharyngeal)
    - NAAT validation

- Consider:
  - HSV serology
  - HAV, HBV → vaccinate as appropriate
  - HCV (especially if HIV infected)
Rectal and Pharyngeal Infections are Commonly Asymptomatic

Proportion of infections that would NOT be identified if only urine/urethral screening is performed among gay/bisexual men

Kent et al. CID 2005

UW PTC STI Self-Testing Program

Information provided with EPT

• Legal in Minnesota since 2008
• Information about medications, allergies & STD
• Advice about complications and need for care (e.g. PID)
• Where to seek care

Expedited Partner Therapy: An effective way to treat partners
Partner Management: Key Points

- Clinical evaluation is first-line option
- Concurrent patient-partner therapy is feasible and effective for many clients
- Expedited partner therapy (EPT) is an option
  - ONLY for GC/CT
  - Safe and effective at reducing reinfection for GC
  - Dual therapy (cefixime 400 mg + azithromycin 1 g)
  - Not recommended for syphilis
  - Consider for trichomonas

**NOT generally recommended for MSM!**
5% of MSM with bacterial STI will be diagnosed with HIV

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The Dreaded Drip:
New diagnostic criteria for urethritis

**Feel the Burn?**
FREESTDCHECK.ORG

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Differential Diagnosis of Urethritis

- Gonococcal Urethritis
  - *Neisseria gonorrhoea*
- Non-Gonococcal Urethritis (NGU)
  - *Chlamydia trachomatis* (15-40%)
  - *Ureaplasma urealyticum*
  - *Mycoplasma genitalium* (15-25%)
  - *Trichomonas vaginalis*
  - Herpes simplex virus
  - Adenovirus
  - Other enteric bacteria
Urethritis

- Diagnostic Considerations
  - Discharge on examination
  - Gram stain ≥ 2 WBCs, methylene blue or gentian violet on urethral secretions
  - Leukocyte esterase on first void urine
- Gram stain not available
  - At least one diagnostic criteria
  - Testing and treatment, gonorrhea/chlamydia
- Symptoms without signs
  - Chlamydia/gonorrhea testing may identify infection
  - Empiric treatment for high risk or unlikely follow-up

Emerging Issues:
*Mycoplasma genitalium*

- Recognized cause of urethritis
  - 30% persistent/recurrent urethritis
- No diagnostic test FDA cleared for use
  - Difficult to culture
  - NAAT available in some large medical centers and commercial laboratories
- Suspect in persistent or recurrent urethritis and consider in persistent cervicitis and PID
  - ? Role in PID/cervicitis
- Treatment implications
  - Azithromycin better than doxycycline, but...
    - Emerging resistance to azithromycin
  - Moxifloxacin for recurrence

Non-Gonococcal Urethritis (NGU) Treatment

- Azithromycin or doxycycline
- Limited data on the public health impact of *M. genitalium* to demote doxycycline
- Persistent or recurrent urethritis
  - *M. genitalium* most common cause
    - Higher azithromycin doses not effective
  - *Trichomonas vaginalis*
    - Metronidazole or tinidazole for men who have sex with women in areas of high prevalence
  - Urology referral with persistence after treatment
Persistent / Recurrent NGU Treatment

**Old Recommendation**
- Metronidazole 2 g orally in a single dose
- OR
- Tinidazole 2 g orally in a single dose
- PLUS
- Azithromycin 1 g orally in a single dose (if not used for initial episode)

**New Recommendation**
- If initially tx’d with doxy → Azithromycin
- If failed azithro → moxifloxacin 400mg qday x 7 days
- If sexually active with women & high trich prevalence → Metronidazole or tinidazole

**Trichomonas vaginalis**
- Test for in women with vaginal discharge
- Consider screening in high prevalence settings (STD clinics, corrections) or asymptomatic persons at high risk
- Lack data if screening/treatment reduces adverse health events or reduces community burden of infection
- Diagnostic testing (NAAT)
  - APTIMA T. vaginalis; BD Probe Tec TV Qx amplified DNA Assay
  - A molecular test-resolved algorithm (negative wet prep followed by NAAT)
- Retesting 3 months after treatment
- Treatment: Metronidazole or Tinidazole 2 gm

**Recurrent Infection is Common**
- Up to 17% at 3 months
- Reinfection from untreated partner: most important!
- Noncompliance with MTZ therapy: less relevant with single-dose observed therapy
- Rescreen women at 3 months (no <2 weeks)
- Ensure partner treatment and avoid sex until all cured
- Infection with MTZ-resistant strain: ~4-10%
  - Tinidazole-resistant ~1%
  - No clear relationship to clinical treatment failure
- Susceptibility testing available if resistance suspected
  - CDC: (404) 718-4141
Gonorrhea antimicrobial resistance: the bug continues to outsmart us

Gonorrhea — Rates of Reported Cases by Age and Sex, United States, 2014

Gonorrhea Infections in Minnesota by Residence at Diagnosis, 2015
Total Number of Cases= 4,097
Age-Specific Gonorrhea Rates by Gender
Minnesota, 2015

Timeline of GC resistance

Gonococcal Isolate Surveillance Project —
United States, 2012
Percentage of urethral Neisseria gonorrhoeae isolates with reduced azithromycin susceptibility,* 2000–2014

Percentage of Neisseria gonorrhoeae isolates with reduced cefixime susceptibility GISP, United States, 2000–2014

Failure of dual therapy for GC

- Case report of man with recent female partner in Japan
- Tested positive for GC urine and pharynx
- Treated with ceftriaxone 500 mg IM and azithromycin 1 gm
- Pharyngeal swab positive at day 15, 79, 98
  - Resistant to azithromycin, ceftriaxone, cefixime, cefotaxime, PCN, tet, cipro
- Treated with ceftriaxone 1 gm and azithromycin 2 gm x 1 at day 98
- TOC negative
### 2015 Updated Gonorrhea Treatment Guidelines

#### Uncomplicated Gonococcal Infection of Cervix, Urethra, or Rectum

<table>
<thead>
<tr>
<th>Recommended Therapy</th>
<th>Alternative Therapy</th>
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<tbody>
<tr>
<td><strong>Ceftriaxone</strong> 250 mg IM x 1</td>
<td><strong>Cefixime</strong> 400 mg PO x 1</td>
</tr>
<tr>
<td><strong>Azithromycin</strong> 1 g PO x 1</td>
<td><strong>Azithromycin</strong> 1 g PO x 1</td>
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</tbody>
</table>

**NOTES:**
- Dose of ceftriaxone now 250 mg (previously 125 mg)
- Doxycycline changed to alternative due to high rate of tetracycline resistance (23.7% in 2013)
- Cefixime NOT first line anymore
- Fluoroquinolones NOT recommended

**Uncomplicated Gonococcal Infection of Cervix, Urethra, or Rectum**

**RECOMMENDED THERAPY**

| Ceftriaxone 250 mg IM x 1 | Azithromycin 1 g PO x 1 |

**NOTES:**
- Alternative regimens for use only when ceftriaxone not available
- Doxycycline changed to alternative due to high rate of tetracycline resistance (23.7% in 2013)
- NOT RECOMMENDED FOR USE IN PHARYNGEAL INFECTION
- If treatment failure, need culture and sensitivity, notify Public Health

**Uncomplicated Gonococcal Infection of Pharynx**

**RECOMMENDED THERAPY**

| Ceftriaxone 250 mg IM x 1 | Azithromycin 1 g PO x 1 |

**NOTES:**
- No alternatives listed
- Test of cure for any other regimen after 14 days
2015 Updated Gonorrhea Treatment Guidelines

**PENICILLIN ALLERGY**
**RECOMMENDED THERAPY**

<table>
<thead>
<tr>
<th>Gentamicin 240 mg IM x 1</th>
<th>+ Azithromycin 2 g PO x 1</th>
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<tr>
<td>OR</td>
<td></td>
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<tr>
<td>Gemifloxacin 320 mg PO x 1</td>
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**NOTES:**
- AZITHROMYCIN 2 gm x 1 with test of cure is NO LONGER RECOMMENDED
- Urogenital infections only
  - Nausea is a common side effect of these regimens

**Managing Treatment Failures**

- Most treatment failure likely due to reinfection
- If suspect treatment failure, obtain culture & susceptibility
  - If reinfection likely (after ceftriaxone/azi): Rx ceftriaxone 250 mg + azithromycin 1 g
  - If reinfection likely (after cefixime/azi): Rx ceftriaxone 250 mg + azithromycin 2 g
  - If treatment failure suspected, gemifloxacin 320 mg + azithromycin 2 g or gentamicin 240 IM + azithromycin 2g
- Report to local or state health department
- Test of cure 7-14 days after retreatment (culture/susceptibility test with NAAT)
- Ensure partner treatment
Syphilis Rates by Stage of Diagnosis
Minnesota, 2005-2015

Primary & Secondary Syphilis Infections in Minnesota by Residence at Diagnosis, 2015

Total Number of Cases = 246

Source: Minnesota Department of Health 2015 STD Surveillance Data Release

Age-Specific Primary & Secondary Syphilis Rates by Gender, Minnesota, 2015

Source: Minnesota Department of Health 2015 STD Surveillance Data Release
Testing: Reverse Screening Algorithm

- Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to guidelines if not previously treated.
- If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units IM x 1 and/or repeat in 2-4 weeks.
- If at risk for syphilis, repeat RPR in 2 to 4 weeks.

CDC Clinical Advisory: Ocular Syphilis Outbreak
February 8, 2016

- 15 cases of ocular syphilis since December 2014 from WA and CA
- Subsequent case finding: >200 cases over 2 years from 20 states
- Most cases among MSM with HIV
  - A few among HIV-negative persons, including heterosexual men and women
- Posterior uveitis and panuveitis most common eye structures involved
- May occur during any stage of syphilis
- Several have resulted in significant sequelae including blindness

Recommended screening for syphilis in pregnant women, MN

- Increase of infectious and latent syphilis cases among women of childbearing age
- 3 cases of congenital syphilis in MN in 2015
  - No cases in 4 years prior
- Devastating effects of congenital syphilis
  - Stillborn
  - Hearing loss, bony abnormalities, lifelong neuro deficits
- Test ALL pregnant women at:
  - First prenatal visit
  - 28 Weeks
  - Delivery
We can prevent HPV and HIV infection with highly effective tools!

Pre Exposure Prophylaxis (PrEP) to prevent HIV acquisition

- A prevention strategy in which a high-risk individual takes a medication regularly (along with continued behavioral risk-reduction strategies) to prevent HIV infection
- Tenofovir-emtricitabine (Truvada) approved for HIV PrEP by the FDA in July 2012
- Added benefits: some protection against HSV and HBV
- May be taken daily or “on demand”
- Consider for MSM, HIV discordant couples, IDU, CSW, recent STI

CDC official guidelines for use of PrEP in MSM, heterosexuals, and IDUs

[Image of CDC guidelines PDF]
Proportion of MSM* Attending STD Clinics with Primary and Secondary Syphilis, Gonorrhea or Chlamydia by HIV Status†, STD Surveillance Network (SSuN), 2012

HPV and the New Guidelines

- Substantially enhanced HPV section
- New guidance on:
  - Prevention/Vaccines
  - Counseling
  - Anogenital Wart (Dx and Tx)
  - Cervical Cancer Screening
  - Anal Cancer Screening
  - HPV related cancers
  - How to manage vaccine series interruption
  - Data on long term safety and efficacy of vaccines

Over 170 types of HPV classified
Updated incidence/prevalence estimates (CDC):
- 14 million new infections per year
- 79 million people infected in the US

*MSM=men who have sex with men
†Excludes all persons for whom there was no laboratory documentation or self-report of HIV status.
‡GC and CT include results from both urethral and urine specimens.
HPV Vaccines

- **Gardasil®**
  - 6, 11
  - Cause 90% genital warts
  - 16, 18, 31, 33, 52, 58
  - Cause 90% Cervical CA

- FDA-approved for females and males 9-26 yrs

- Quadrivalent vaccine (4vHPV) will be phased out

- Current recommendation:
  - 3 dose schedule: 0, 2, 6 months
  - 2 dose regimen with alternative dosing schedule (0, 6 mo or 0, 12 mo) is being evaluated – stay tuned

HPV Vaccine Recommendations

- Routine vaccination at age 11 or 12 years*

- Recommended through age 26 for females and through age 21 for males not previously vaccinated

- Recommended for men who have sex with men and immunocompromised men (including persons HIV-infected) through age 26

- Vaccination of females is recommended with 2vHPV, 4vHPV, or 9vHPV

- Vaccination of males is recommended with 4vHPV or 9vHPV

* Vaccination series can be started at any age

"The near disappearance of warts" in Australia

- National HPV vaccination program in Australia since 2007
  - FREE vaccination to women 12-26 yo, 70% coverage

- Prevalence of warts evaluated in large STD Clinic 2004-2011

- Wart prevalence decreased dramatically

<table>
<thead>
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<th>2007-2008</th>
<th>2008-2011</th>
<th>OR</th>
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<tbody>
<tr>
<td>Women &lt;21 yo</td>
<td>18.6%</td>
<td>1.9%</td>
<td>0.44</td>
</tr>
<tr>
<td>Heterosexual men &lt;21 yo</td>
<td>22.9%</td>
<td>2.9%</td>
<td>0.42</td>
</tr>
</tbody>
</table>

- But no change in heterosexual women or men >30 yo, MSM, or non-residents
HPV prevalence in the vaccine era: USA

- Vaccine recommended for females since 2006
- Prevalence in cervicovaginal specimens measured pre vaccine (2003-2006) and vaccine (2009-12) (NHANES)
- Measured HPV-6, -11, -16, -18 (quadrivalent vaccine)
  - Prevalence declined 64% in 14-19 year old females
    - (11.5%→4.3%)
  - Prevalence declined 34% in 20-24 year old females
    - (18.5→12.1%)
  - Despite low coverage:
    - 51% of 14-19 year old females received one dose 2009-12
    - 35% received 3 doses

HPV Coverage in 2015

Improving HPV vaccine coverage:
Educating patients and families

- HPV vaccine is very safe
- HPV vaccine is the best way to prevent many types of cancer
- HPV vaccine reduces HPV disease
- HPV vaccine is part of the routine adolescent immunization platform
  - Covered by insurance or Vaccine for Children (VFC)
- HPV vaccine is most effective when given at younger ages
  - Stronger immune response
  - Prior to exposure
- De-emphasize messaging around sexual transmission of HPV
Hepatitis C: now available via sex, drugs, and rock-n-roll

Sexual Transmission of Hepatitis C

Acute HCV in HIV-infected MSM in New York City
- 2005-2010, total of 74 HIV-infected MSM with recently acquired HCV referred to Mt Sinai Medical Center
- None had reported history of injection drug use
- Most were asymptomatic – infection detected by AST/ALT abnormalities
- Risk factors for acute sexually-acquired HCV infection:
  - Receptive anal intercourse with no condom & with ejaculation of partner (adjusted odds ratio [aOR] = 23)
  - Sex while using methamphetamine (aOR = 28.6)
- Other risk factors:
  - Seroconverting
  - Group sex
  - Cocaine use
  - Other non-IDU
  - Use of sex toys
  - Concurrent STDs
HCV Screening Recommendations in HIV

- All HIV-infected persons
- At initial evaluation
- Consider repeat annually

- More frequent testing
- High community HCV prevalence and incidence
- High-risk sexual behavior
- Concomitant ulcerative STDs and STD-related proctitis
- Drug use, especially IDU and methamphetamine

Zika Virus: The newest STI

- Mosquito-borne flavivirus
- Outbreak in S/Central Americas
  - First cases now in Florida
- Association with congenital microcephaly
- Sexual transmission described in multiple case reports
Zika: Aedes vector

- *Aedes aegypti* & *Aedes albopictus*
- Favors urban habitats
- Carrier of other flaviviruses
- Daytime biters
- Environment:
  - Tropical and subtropical

Rapidly expanding geographic area

Zika cases in the USA, August 31, 2016

- 2687 travel associated cases
- 35 locally acquired cases (all in Florida)
- 13,791 locally acquired cases in Puerto Rico
Emerging STIs: ZIKA

- Zika can be sexually transmitted from a person who has Zika to his or her sex partners, even while they are not symptomatic.
  - Transmission from M→F, F→M, M→M
- Sex includes vaginal, anal and oral sex, and the sharing of sex toys.
- All pregnant women with sex partners who live in or traveled to an area with Zika should use barrier methods during sex or abstain from sex for the remainder of their pregnancy.
- All other couples in which a partner has been in an area with Zika can also reduce the risk of sexual transmission by using barrier methods or abstaining from sex.
  - Barriers include male and female condoms and dental dams
  - To be effective, barrier methods must be used from start to finish, every time during vaginal, anal and oral sex.

Zika: How long are barrier methods or abstinence recommended?

- At least 8 weeks after a Zika diagnosis or start of symptoms if the traveling partner is female or if the traveling partner (male or female) has no symptoms.
- At least 6 months after a Zika diagnosis or start of symptoms if the traveling partner is male. This long extended period is because Zika stays in semen longer than in other body fluids.

Interim guidance for health care providers

Health care providers should:
- Test all pregnant women who may have been exposed to Zika sexually (i.e., had sexual contact without a barrier method with a person who lives in or has traveled to an area with Zika).
- Test any patients for Zika if they develop symptoms of Zika and report potential sexual exposure to a partner who lives in or traveled to an area with Zika.
- Zika testing to assess the risk of sexual transmission is **NOT** recommended
- These guidelines are likely to change as we learn more about Zika virus
Zika Testing: Symptomatic Persons

- **Virologic testing**
  - Reverse transcription PCR testing for Zika RNA
  - Test samples: Serum and urine
  - Test within 2 weeks of symptoms onset — or-
  - If positive, no antibody testing is needed
  - If negative, test for Zika IgM

- **Serologic testing**
  - Zika virus specific IgM
    - Positive results 4 days to 12 weeks post illness
  - Plaque reduction neutralization test
    - Confirmatory test for positive, equivocal or inconclusive IgM tests

Testing in Pregnant Women with Exposure

- All pregnant women should be assessed for Zika at each prenatal care visit. They should be asked if they:
  - Traveled to or live in an area with active Zika transmission
  - Had sex without a condom or other barrier method to prevent infection with a partner who lives in or traveled to an area with active Zika transmission
  - If yes to either, testing should be performed

Diagnosis of Zika in Pregnant Women

Viroligic testing
- Reverse transcription PCR testing for Zika RNA
- Test samples: Serum and urine
  - Within 2 weeks of last possible exposure
  - For women with positive IgM testing
  - If PCR positive, no antibody testing is needed
  - If negative, test for Zika IgM

Serologic testing
- Zika virus specific IgM
  - Perform for women first presenting 2-12 weeks following exposure
  - For women in areas with active Zika transmission, perform IgM testing in 1st and 2nd trimester
  - RT-PCR testing for women who are IgM positive

Outstanding questions: Sexual transmission

- How often do persons with asymptomatic Zika infection pass Zika through sex?
- Does sexual transmission of Zika pose a different risk of birth defects than mosquito-borne transmission?
- How long after infection can Zika virus be sexually transmitted?

Conclusions

- STIs are on the rise with ever-changing epidemiology
  - Increasing chlamydia rates
  - Syphilis in women of child bearing age
- Screen, appropriately!
  - GC/Chlamydia screening in women>=25
  - Extragential screening in MSM, frequency based on risk
- Gonococcal antimicrobial resistance continues to be a challenge
- Mycoplasma genitalium is an emerging pathogen
  - NGU
  - Moxifloxacin>Azithromycin>Doxycycline
- Prevention works! Share HPV vaccine and PrEP with your patients
  - Identify and educate
- New viral STIs - stay tuned (HCV, Zika)

Want to know more about STDs? There’s an app for that.

- CDC Treatment Guidelines App for Apple and Android
- (Search for “STD Tx”)
STD Resources

- University of WA STD Prevention Training Center
  - www.uwptc.org
- National Network of STD/HIV Prevention Training Centers
  - www.nnptc.org
- CDC Treatment Guidelines
  - www.cdc.gov/std/treatment
- American Social Health Association (ASHA) booklets, books, handouts, the Helper
  - www.ashastd.org
  - (800) 230-6039

STD Clinical Consultation Network (STDCCN)

- Provides STD clinical consultation services within 1-3 business days, depending on urgency, to healthcare providers nationally
- Your consultation request is linked to your regional PTC’s expert faculty
- We are just a click away! www.STDCCN.org