Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed treatment of 3 common bacterial sexually transmitted infections (STIs) including gonorrhea, chlamydia and syphilis at the April 2021 meeting. This review follows the release by the Department of Health and Human Services (HHS) of the first-ever “STI National Strategic Plan” in December 2020.1 Also, the Centers for Disease Control and Prevention (CDC) updated the 2015 STI Treatment guidelines in December 2020 with changes in treatment of gonorrhea with particular attention to antimicrobial stewardship and changing antimicrobial resistance patterns in gonorrhea isolates.2 The NPTC considered the treatment of gonorrhea, chlamydia, and syphilis as a result of these two developments and the disparate impact of STIs among American Indian/Alaska Native (AI/AN) people3. As a result of this review, the NPTC voted to ADD (1) ceftriaxone, (2) cefixime, for outpatient treatment of gonorrhea in the case of EPT or when injection therapy is not possible, (3) azithromycin, (4) doxycycline, and (5) penicillin G benzathine injection to the National Core Formulary.

Discussion:
The incidence of STIs is increasing nationally and among AI/AN populations. Chlamydia cases continued to rise in 2019, up 19% from 2015. Gonorrhea rates are up 56% from 2015 to 2019. AI/AN people rank 2nd in incidence of these conditions among all racial & ethnic groups. Syphilis rates are up 74% from 2015 to 2019 with AI/AN females ranking first among racial and ethnic groups. Congenital syphilis also finds AI/AN cases first among all racial and ethnic groups with rates in 2019 increasing 13-fold from the level in 2015. Impacts of STI include infertility, pelvic inflammatory disease, and preterm labor, as well as adverse birth outcomes among pregnant women with STIs including: neonatal ophthalmologic infection, chlamydia pneumonia, premature delivery, low birth weight, fetal demise, and neonatal death. Minimal symptoms among persons with STIs is a key factor leading to increased risk for transmission, and a reason to promote screening and timely treatment wherever appropriate. Finally, presence of bacterial STI increases likelihood of HIV transmission such that STI diagnosis warrants both HIV screening and evaluation for potential use of HIV pre-exposure prophylaxis (PrEP).

HHS STI Strategic Plan
The HHS Strategic Plan for STI was reviewed at the meeting.1 The HHS plan identifies AI/AN communities as a subgroup that is disproportionately impacted by STIs. The plan has five goals with specific metrics. The goals are considered areas in need of improvement and are:
1. Prevent new STIs by reducing stigma; increase HPV immunization, integrate STI prevention in HIV, viral hepatitis, and substance use disorder services.
2. Improve the health of people by reducing adverse outcomes of STIs, improving the workforce through training including alternate site testing, special populations assessment, expedited partner therapy, and partner notification.
3. Accelerate progress in STI research, technology, and innovation in vaccines, new drugs, diagnostic testing, antibiotic resistance/sensitivity assessment, chemoprophylaxis.
4. Reduce STI-related health disparities through policy, training around health inequities, and stigma reduction.
5. Achieve integrated, coordinated efforts that address the STI epidemic in related policies, data collection and dissemination, and action plans across agencies.

The HHS STI Strategic plan include metrics and indicators with 5- and 10-year targets. The plan outlines a specific indicator to decrease congenital syphilis among AI/AN and also includes 3 development indicators. These indicators are:
1. Increase the percentage of patients with gonorrhea who are treated with a recommended regimen.
2. Increase the percentage of patients with syphilis who are treated with a recommended regimen.
3. Increase extra-genital chlamydia and gonorrhea screening among MSM.

Specific implementation plans for the IHS are under development.

CDC Gonorrhea Treatment Guidelines
The CDC guideline update for gonorrhea treatment centers on elimination of the recommendation of dual therapy for gonorrhea.2 The update is based on changing antimicrobial resistance patterns. Since 2015, gonorrhea resistance patterns, as monitored through the Gonorrhea Isolate Surveillance Project (GISP), shows rising resistance to azithromycin and declining resistance to ceftriaxone.4 The recommended dose of ceftriaxone has been increased to provide increased time of the drug concentration above the MIC for gonorrhea at the most common anatomical sites of infection. A weight-based dose consideration has also been added to further address the time with drug concentrations above MIC for larger patients. Finally, the recommendation of a test-for-cure was added to the guideline for oropharyngeal gonorrhea
treatment. The oropharynx is the site where gonorrhea resistance is most likely to arise given anatomic considerations of the oropharynx and their impact on pharmacokinetics.

Chlamydia treatment was also addressed due to the impact of elimination of dual therapy for gonorrhea and the frequent situation of coinfection or empiric therapy-situations when dual coverage is desirable. When co-infection with gonorrhea and chlamydia is considered or when empiric therapy is administered, the recommendation is to treat chlamydia with doxycycline 100mg PO BID for 7 days. Azithromycin remains first line for chlamydia in patients with test-proven chlamydia alone and among pregnant women in whom doxycycline is contraindicated. Clinicians may also choose to utilize azithromycin for chlamydia coverage or empiric therapy when adherence to the 7-day course of doxycycline is in doubt.

Syphilis treatment recommendations remain unchanged. Syphilis rates in AI/AN women and newborns are the highest of any racial or ethnic group in the US. Most states require syphilis screening at presentation of all pregnant people. The Indian Health Manual requires syphilis screening twice in pregnancy, first at presentation and a second test in the third trimester. Many states require an additional syphilis screen when a woman presents in labor. Given the high rates of congenital syphilis among AI/AN women, three-time point screening during pregnancy is appropriate: (1) screening at first prenatal visit (ideally first trimester), (2) again during the third trimester, and (3) on admission for delivery. It is also important that pregnant women be screened for HIV, chlamydia and gonorrhea during pregnancy and that all people with any STI get syphilis and HIV screening as part of their evaluation.

Expedited partner therapy (EPT) is the practice of providing partner treatment to a patient for them to deliver to their partner(s) when they are agreeable. EPT can also be administered to a partner if they are present at the time a patient is treated. EPT has been shown to reduce the rate of reinfection in people with gonorrhea and chlamydia, to be cost effective, and has been found to be likely beneficial in IHS settings.5-7

The CDC’s gonorrhea treatment updates impacted EPT recommendations; namely, the dose of ceftriaxone for gonorrhea EPT was increased to 800 mg PO once, and the addition of doxycycline 100 mg PO bid for 7 days to EPT was recommended when chlamydia co-infection has not been excluded. Changes were consistent with the gonorrhea treatment update. The CDC recommends this practice generally be excluded with men who have sex with men (MSM) due to concerns over higher rates of other STIs (syphilis and HIV) and the need for testing. EPT is strongly encouraged as a means to reduce re-infection, is legal in most states, & considered acceptable within IHS for non-beneficiary partners.7

Findings:

The NPTC voted to add ceftriaxone, cefixime (for outpatient treatment of gonorrhea in the case of EPT or when injection therapy is not possible), azithromycin, doxycycline, and benzathine penicillin injection to the National Core Formulary.

- Ceftriaxone 500 mg IM once for patients weighing <150kg and ceftriaxone 1000 mg IM once for patients >150 kg is the preferred treatment for gonorrhea.
- Azithromycin 1000mg once is the preferred treatment for chlamydia when gonorrhea testing is confirmed negative. Doxycycline 100 mg PO BID for 7 days can also be used (and is preferred with gonorrhea co-infection, or empiric treatment that includes ceftriaxone or cefixime).
- Cefixime 800 mg PO once is considered the preferred agent for gonorrhea EPT when the partner is not present for ceftriaxone injection and EPT is to be delivered by the patient to their partner(s).
- Gonorrhea and chlamydia co-infection treatment is recommended with ceftriaxone and oral doxycycline. Avoiding azithromycin is recommended when treating coinfection or empiric treatment of urethritis before test results are available.
- Follow up testing for gonorrhea and chlamydia is recommended for all patients within 3 months.
- Test of cure within 7-14 days is recommended for all cases of oropharyngeal gonorrhea. If a follow up test-of-cure is positive, consultation of CDC guidelines for further management is recommended due to likelihood of antibiotic resistant gonorrhea.
- All patients with a positive STI test or concerns for any STI should be tested for HIV and syphilis.
- All patients requesting STI testing should be offered oropharyngeal and anal gonorrhea and chlamydia testing.
- MSM should be tested for chlamydia and gonorrhea at oropharyngeal, urethral and rectal sites presumptively and syphilis and HIV testing should be completed at minimum once per year and more often based on sexual risk.
- MSM presenting with an STI concern should be offered PrEP (HIV pre-exposure prophylaxis)
- Outpatient treatment of syphilis is dependent on staging:
  - primary/secondary/early latent syphilis should be treated with benzathine penicillin 2.4 Million units IM once.
  - late latent/latent of unknown duration syphilis treatment is benzathine penicillin 2.4M units IM on day 0, day 7, and day 14.
If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References: