STI Treatment Guidelines

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Training course in sexually transmitted infections, HIV/AIDS 2018

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STI treatment guidelines

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- Genital herpes simplex
- *Treponema pallidum* (syphilis)
- Syphilis screen and treat for pregnant women
Rationale

- STI guidelines last updated in 2003
- Concerns about STI syndromic case management
- Treatment issues related to antimicrobial resistance in *N. gonorrhoeae*
- Scaling up syphilis screening – increasing availability of rapid syphilis test, testing flowcharts
### STI guidelines: Prevention, Management and Control

<table>
<thead>
<tr>
<th>Phases</th>
<th>Topics</th>
<th>Timeframe</th>
</tr>
</thead>
</table>
| **Phase 1**   | **Treatment of specific STIs:** Chlamydia trachomatis (chlamydia), Neisseria gonorrhoeae (gonorrhoea), HSV-2 (genital herpes) and Treponema pallidum (syphilis)  
Syphilis screening and treatment of pregnant women  
STI syndromic approach  
May 2016 – December 2017 |
| **Phase 2**   | **STI prevention:** condoms, behaviour change  
communication, biomedical interventions and vaccines | 2017–2018 |
| **Phase 3**   | **Treatment of specific STIs and reproductive tract infections** (RTIs) not addressed in Phase 1: Trichomonas vaginalis (trichomoniasis), bacterial vaginosis, Candida albicans (candidiasis), Hemophilus ducreyi (chancroid), Klebsiella granulomatis (donovanosis), human papillomavirus (HPV; genital warts/cervical cancer), Sarcopes scabei (scabies) and Phthirus pubis (pubic lice) | 2017–2018 |
| **Phase 4**   | **STI laboratory diagnosis and screening**                             | 2017–2018 |
WHO STI Guidelines

Non-infected: Primary prevention

Infected

Asymptomatic

Symptomatic

Syphilis screening

Screening

Presumptive treatment

Syndromic management

Laboratory diagnosis

Partner management

Effective treatment

Operational issues
Objective of the guidelines

- Provide evidence-based guidance on treatment of specific STI *N. gonorrhoeae*, *Chlamydia trachomatis* and *Treponema pallidum* and syphilis screening and treatment for pregnant women
- Support countries to update their national guidelines
Target audience

- Health-care providers at all levels (primary, secondary and tertiary) of the health-care system
- Individuals working in sexual and reproductive health programmes, such as HIV/AIDS, family planning, maternal and child health and adolescent health
- Policy-makers, managers, programme officers and other professionals implementing STI management interventions at regional, national and subnational levels.
Guideline Development Group

- WHO Steering Committee – from different WHO departments and representation from regions
  - Inventory of existing guidelines
  - Determine the need for an updated guideline
  - Draft initial PICO

- STI guideline development group – 33 STI experts with different expertise
  - 4 subgroups to focus on specific STIs
  - Finalize the scoping document – PICO methods
  - Involve in the entire process of guideline development

- STI external development group – 15-18 STI experts
  - Reviewed the final document
Review of evidence

- PICO question and components - benefits, harms, patient values, acceptability, feasibility, equity and costs
- Search terms and search strategies developed
- Pre-existing evidence
  - Previously published guidelines that included systematic reviews of the literature
  - Existing systematic reviews
    - Cochrane Library suite of databases (Cochrane Database of Systematic Reviews [CDSR], Database of Abstracts of Reviews of Effects [DARE], Health Technology Assessment [HTA] database and the American College of Physicians [ACP] Journal Club)
- New systematic review of randomized controlled trials (RCTs) and non-randomized studies
GRADE

- Evidence Profile
- Evidence to decision framework
- Making recommendations
  - STI GDG group
  - Follow-up teleconferences
Assessment of quality/certainty of the evidence at four levels

- **High** – We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate** – We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low** – Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low** – We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.
### Implication of strong and conditional recommendations using the GRADE approach

<table>
<thead>
<tr>
<th>Implications</th>
<th>Strong recommendation “The WHO STI guideline recommends...”</th>
<th>Conditional recommendation “The WHO STI guideline suggests...”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For patients</strong></td>
<td>Most individuals in this situation would want the recommended course of action, and only a small proportion would not.</td>
<td>The majority of individuals in this situation would want the suggested course of action, but many would not.</td>
</tr>
<tr>
<td></td>
<td>Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</td>
<td></td>
</tr>
<tr>
<td><strong>For clinicians</strong></td>
<td>Most individuals should receive the recommended course of action.</td>
<td>Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual’s values and preferences.</td>
</tr>
<tr>
<td></td>
<td>Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.</td>
<td>Decision aids may be useful to help individuals make decisions consistent with their values and preferences.</td>
</tr>
<tr>
<td><strong>For policy-makers</strong></td>
<td>The recommendation can be adopted as policy in most situations.</td>
<td>Policy-making will require substantial debate and involvement of various stakeholders.</td>
</tr>
</tbody>
</table>
NEISSERIA GONORRHOEA

Key Messages: *N. gonorrhoea*

- Local resistance data to determine the choice of therapy (both for dual therapy and single therapy).
- Use of dual therapy over single therapy
  - Ceftriaxone 250 mg or Cefixime 400 mg plus Azithromycin 1 gram
- Quinolones are no longer recommended
- Oropharyngeal infection
- Treatment Failure: increase dose
  - Ceftriaxone 500 mg plus Azithromycin 2 grams
  - Gentamicin or Spectinomycin plus Azithromycin 2 grams
- For all neonates, topical ocular prophylaxis for the prevention of gonococcal and chlamydial ophthalmia neonatorum.
Genital and anorectal gonococcal infections

The WHO STI guideline recommends that local resistance data should determine the choice of therapy (both for dual therapy and single therapy).

**Good practice statement**

In settings where local resistance data are not available, the WHO STI guideline suggests dual therapy over single therapy for people with genital or anorectal gonorrhoea.

- **Dual therapy** (one of the following)
  - ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose
  - cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose

- **Single therapy** (one of the following, based on recent local resistance data confirming susceptibility to the antimicrobial)
  - ceftriaxone 250 mg IM as a single dose
  - cefixime 400 mg orally as a single dose
  - spectinomycin 2 g IM as a single dose.

*Conditional recommendation, very low quality evidence*
Oropharyngeal gonococcal infections

In adults and adolescents with gonococcal oropharyngeal infections, the WHO STI guideline suggests dual therapy over single therapy.

- **Dual therapy** (one of the following)
  - ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose
  - cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose

- **Single therapy** (based on recent local resistance data confirming susceptibility to the antimicrobial)
  - ceftriaxone 250 mg IM as single dose.

*Conditional recommendation, low quality evidence*
Retreatment of gonococcal infections after treatment failure

In people with gonococcal infections who have failed treatment, the WHO STI guideline suggests the following options.

- If reinfection is suspected, re-treat with a WHO-recommended regimen, reinforce sexual abstinence or condom use, and provide partner treatment.
- If treatment failure occurred after treatment with a regimen not recommended by WHO, re-treat with a WHO-recommended regimen.
- If treatment failure occurred and resistance data are available, re-treat according to susceptibility.
- If treatment failure occurred after treatment with a WHO-recommended single therapy, re-treat with WHO-recommended dual therapy.
- If treatment failure occurred after a WHO-recommended dual therapy, re-treat with one of the following dual therapies:

  Conditional recommendation, very low quality evidence
Retreatment of gonococcal infections after treatment failure (dual therapy options)

- ceftriaxone 500 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
- cefixime 800 mg orally as a single dose PLUS azithromycin 2 g orally as a single dose
- gentamicin 240 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
- spectinomycin 2 g IM as a single dose (if not an oropharyngeal infection) PLUS azithromycin 2 g orally as a single dose.

*Conditional recommendation, very low quality evidence*
Gonococcal ophthalmia neonatorum

In neonates with gonococcal conjunctivitis, the WHO STI guideline suggests one of the following treatment options:

- ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose
- kanamycin 25 mg/kg (maximum 75 mg) IM as a single dose
- spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose.

*Conditional recommendation, very low quality evidence*
Prevention of gonococcal and chlamydial ophthalmia neonatorum.

- For all neonates, the WHO STI guideline recommends topical ocular prophylaxis for the prevention of gonococcal and chlamydial ophthalmia neonatorum.  
  **Strong recommendation, low quality evidence**

- For ocular prophylaxis, the WHO STI guideline suggests one of the following options for topical application to both eyes immediately after birth:
  - tetracycline hydrochloride 1% eye ointment
  - erythromycin 0.5% eye ointment
  - povidone iodine 2.5% solution (water-based)
  - silver nitrate 1% solution
  - chloramphenicol 1% eye ointment.  
  **Conditional recommendation, low quality evidence**

**Chlamydia trachomatis**
Key Messages: C. trachomatis and LGV

- **C. trachomatis**
  - Azithromycin or Doxycycline remain to be treatment of choice
  - Ano-rectal infection: Doxycycline over Azithromycin

- **Lymphogranuloma venereum**
  - Doxycycline 100 mg orally twice daily for 21 days over azithromycin 1 g orally, weekly for 21 days
Uncomplicated genital infection

The WHO STI guideline suggests treatment with one of the following options:
- azithromycin 1 g orally as a single dose
- doxycycline 100 mg orally twice a day for 7 days

or one of these alternatives:
- tetracycline 500 mg orally four times a day for 7 days
- erythromycin 500 mg orally twice a day for 7 days
- ofloxacin 200–400 mg orally twice a day for 7 days.

*Conditional recommendation, moderate quality evidence*
Ano-rectal infection

The WHO STI guideline suggests treatment with doxycycline 100 mg orally twice a day for 7 days over azithromycin 1 g orally as a single dose.

*Conditional recommendation, low quality evidence*
Genital infection in pregnant women

- Azithromycin over erythromycin
  *Strong recommendation, moderate quality evidence*

- Azithromycin over amoxicillin.

- Amoxicillin over erythromycin.
  *Conditional recommendation, low quality evidence*

- Dosages:
  - azithromycin 1 g orally as a single dose
  - amoxicillin 500 mg orally three times a day for 7 days
  - erythromycin 500 mg orally twice a day for 7 days.
Lymphogranuloma venereum

The WHO STI guideline suggests treatment with doxycycline 100 mg orally twice daily for 21 days over azithromycin 1 g orally, weekly for 3 weeks.

*Conditional recommendation, very low quality evidence*
Neonatal conjunctivitis

- Azithromycin 20 mg/kg/day orally, one dose daily for 3 days, over erythromycin 50 mg/kg/day orally, in four divided doses daily for 14 days.

*Strong recommendation, very low quality evidence*
Treponema pallidum (syphilis)

### Key Message: Early syphilis (primary, secondary, early latent < 2 years)

<table>
<thead>
<tr>
<th>Drug of Choice</th>
<th>Adults and Adolescents</th>
<th>Pregnant Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzathine penicillin G</td>
<td>Benzathine penicillin G 2.4 million units IM QD x 1</td>
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</tr>
<tr>
<td></td>
<td>Procaine penicillin G 1.2 million units IM QD x 10-14 days</td>
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</tr>
<tr>
<td>Penicillin allergy or</td>
<td>Doxycycline 100 mg BID x 14 days or Ceftriaxone 1 g IM, QD x 14 days or in special circumstances Azithromycin 2 g QD x 1</td>
<td>Erythromycin 500 mg QID x 14 days* or Ceftriaxone 1 g IM, QD x 10-14 days* or in special circumstances Azithromycin 2 g QD x 1*</td>
</tr>
<tr>
<td>stock out</td>
<td></td>
<td>*with caution</td>
</tr>
</tbody>
</table>

*with caution*
Early syphilis (primary, secondary, early latent < 2 years) in adults and adolescents

- Benzathine penicillin G 2.4 million units once intramuscularly over no treatment.
  *Strong recommendation, very low quality evidence*

- Benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin G 1.2 million units 10-14 days intramuscularly

- When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy) or are not available (e.g. due to stock outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 14 days or ceftriaxone 1 g intramuscularly once daily for 10-14 days or in special circumstances azithromycin 2 g once orally.
  *Conditional recommendation, very low quality evidence*
Early syphilis (primary, secondary, early latent < 2 years) in pregnant women

- Benzathine penicillin G 2.4 million units once intramuscularly over no treatment.
  
  *Strong recommendation, very low quality evidence*

- Benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin 1.2 million units intramuscularly once a day for 10 days.

- When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 14 days or ceftriaxone 1 g intramuscularly once daily for 10-14 days or azithromycin 2 g once orally.

  *Conditional recommendation, very low quality evidence*
Key Message: LATE SYPHILIS (infection of more than two years’ duration without evidence of treponemal infection)

<table>
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<tr>
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<tbody>
<tr>
<td><strong>Drug of Choice</strong></td>
<td>Benzathine penicillin G 2.4 million units IM QD x 3 consecutive weeks</td>
<td>Benzathine penicillin G 2.4 million units IM QD x 3 consecutive weeks</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>Procaine penicillin G 1.2 million units IM QD x 10-20 days</td>
<td>Procaine penicillin G 1.2 million units IM QD x 20 days</td>
</tr>
<tr>
<td><strong>Penicillin allergy or stock out</strong></td>
<td>Doxycycline 100 mg BID x 30 days</td>
<td>Erythromycin 500 mg QID x 30 days (with caution)</td>
</tr>
</tbody>
</table>

Because syphilis during pregnancy can lead to severe adverse complications to the fetus or newborn, **stock-outs of benzathine penicillin for use in antenatal care should be avoided.**
LATE SYPHILIS (infection of more than two years’ duration without evidence of treponemal infection)
Adults and adolescents

- Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment
  
  *Strong recommendation, very low quality evidence*

- Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units once a day for 20 days

- When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (due to stock outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 30 days.

  *Conditional recommendation, very low quality evidence*
LATE SYPHILIS (infection of more than two years’ duration without evidence of treponemal infection)

Pregnant women

- Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment
  
  *Strong recommendation, very low quality evidence*

- Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units once a day for 20 days

- When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (due to stock outs), the WHO STI guideline suggests *with caution* using erythromycin 500 mg orally four times daily for 30 days.

  *Conditional recommendation, very low quality evidence*
Key Message: Congenital syphilis

- In infants with confirmed congenital syphilis or infants who are clinically normal, but mother with syphilis was not treated, inadequately treated (including treated within 30 days of delivery) or treated with non-penicillin regimen:
  - Aqueous benzyl penicillin 100,000-150,000 U/kg/day intravenously for 10-15 days
  - Procaine penicillin 50,000 U/kg/day single dose intramuscularly for 10-15 days

- In infants who are clinically normal and the mother had syphilis and was adequately treated with no signs of re-infection:
  - closely monitor the infants over treatment
  - Benzathine penicillin G 50,000 U/kg/day single dose intramuscularly
Infants

In infants with confirmed congenital syphilis or infants who are clinically normal, but mother with syphilis was not treated, inadequately treated (including treated within 30 days of delivery) or treated with non-penicillin regimen, the WHO STI guideline suggests aqueous benzyl penicillin or procaine penicillin.

Dosages:
- Aqueous benzyl penicillin 100,000-150,000 U/kg/day intravenously for 10-15 days
- Procaine penicillin 50,000 U/kg/day single dose intramuscularly for 10-15 days

*Conditional recommendation, very low quality evidence*
Infants

- In infants who are clinically normal and the mother had syphilis and was adequately treated with no signs of re-infection, the WHO STI guideline suggests to closely monitor the infants over treatment.  
  *Conditional recommendation, very low quality evidence*

- Treatment: benzathine penicillin G 50,000 U/kg/day single dose intramuscularly
Genital herpes simplex virus

# Key Messages: Genital Herpes Simplex Virus

<table>
<thead>
<tr>
<th>Primary</th>
<th>Episodic</th>
<th>Suppressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir 400 mg TID x 10 days</td>
<td>Acyclovir 400 mg TID x 5 days</td>
<td>Acyclovir 400 mg BID</td>
</tr>
<tr>
<td>Acyclovir 200 mg 5 x day x 10 days</td>
<td>Acyclovir 800 mg BID x 3 day</td>
<td>Valacyclovir 500 mg BID x 3 days</td>
</tr>
<tr>
<td>Valacyclovir 500 mg BID x 10 days</td>
<td>Acyclovir 800 mg TID x 2 days</td>
<td>Famciclovir 250 mg BID</td>
</tr>
<tr>
<td>Famciclovir 250 mg TID x 7-10 days</td>
<td>Valacyclovir 500 mg BID x 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Famciclovir 250 mg TID x 5 days</td>
<td></td>
</tr>
</tbody>
</table>

**Suppressive therapy:** Individuals who have frequent recurrences (such as four to six times per year or more), severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy.

**PLHIV:** increase dosages for episodic and suppressive therapy.
**Key Messages: Genital Herpes Simplex Virus HIV positive and immunocompromise**

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<td>Acyclovir 200 mg 5 x day x 10</td>
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</tr>
<tr>
<td>days</td>
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<td>Famciclovir 500 mg BID</td>
</tr>
<tr>
<td>Valacyclovir 500 mg  BID x 10</td>
<td></td>
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</tr>
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**Suppressive therapy:** Individuals who have frequent recurrences (such as four to six times per year or more), severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy.

**PLHIV:** increase dosages for episodic and suppressive therapy
First clinical episode of genital HSV infection

- Treatment over no treatment.  
  *Strong recommendation, moderate quality evidence*

- Standard dose of acyclovir over valacyclovir or famciclovir.

Dosages:
- Acyclovir 400 mg orally 3 times a day for 10 days (standard dose)
- Acyclovir 200 mg orally 5 times a day for 10 days
- Valacyclovir 500 mg orally twice a day for 10 days
- Famciclovir 250 mg orally 3 times a day for 10 days  
  *Conditional recommendation, moderate quality evidence*
Recurrent clinical episode of genital HSV infection (episodic therapy)

- Treatment over no treatment
- Acyclovir over valacyclovir or famciclovir.

Dosages:
- Acyclovir 400mg orally three times a day for 5 days, 800mg twice a day for 5 days, or 800mg three times a day for 2 days
- Valacyclovir 500 mg orally twice a day for 3 days
- Famciclovir 250 mg orally twice a day for 5 days

*Conditional recommendation, moderate quality evidence*
Recurrent clinical episode of genital HSV infection (episodic therapy)

Dosages for people living with HIV and people who are immunocompromised

- Acyclovir 400mg orally three times a day for 5 days
- Valacyclovir 500 mg orally twice a day for 5 days
- Famciclovir 250 mg orally twice a day for 5 days

*Conditional recommendation, moderate quality evidence*
Recurrent clinical episodes of genital HSV infections that are frequent, severe or cause distress (suppressive therapy)

- Suppressive therapy over episodic therapy
  *Conditional recommendation, moderate quality evidence*
- Acyclovir over valacyclovir or famciclovir for suppressive therapy.

**Dosages:**
- Acyclovir 400mg orally twice a day
- Valacyclovir 500mg orally once a day
- Famciclovir 250 mg orally twice a day
  *Conditional recommendation, low quality evidence*
Recurrent clinical episodes of genital HSV infections that are frequent, severe or cause distress (suppressive therapy)

Dosages for people living with HIV and people who are immunocompromised
- Acyclovir 400mg orally twice a day
- Valacyclovir 500mg orally twice a day
- Famciclovir 500 mg orally twice a day

Conditional recommendation, low quality evidence