# CHALLENGES WITH DRUG RESISTANT SEXUALLY TRANSMITTED INFECTIONS


ANWAR HOOSEN

Department of Medical Microbiology

University of Pretoria


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Global Antibiotic Resistance Partnership

CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

# SEXUALLY TRANSMITTED INFECTIONS

# AETIOLOGICAL AGENTS

## BACTERIA

- ***Neisseria gonorrhoeae***
- ***Chlamydia trachomatis***
- ***Treponema pallidum***
- ***Haemophilus ducreyi***
- ***Calymmatobacterium granulomatis***

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- ***Gardnerella vaginalis***
- ***Ureaplasma urealyticum***
- ***Mycoplasma hominis***
- ***Mycoplasma genitalium***

## VIRUSES

- **HIV**
- **HSV**
- **HPV**
- **HBV**

## PARASITES

- ***Trichomonas vaginalis***

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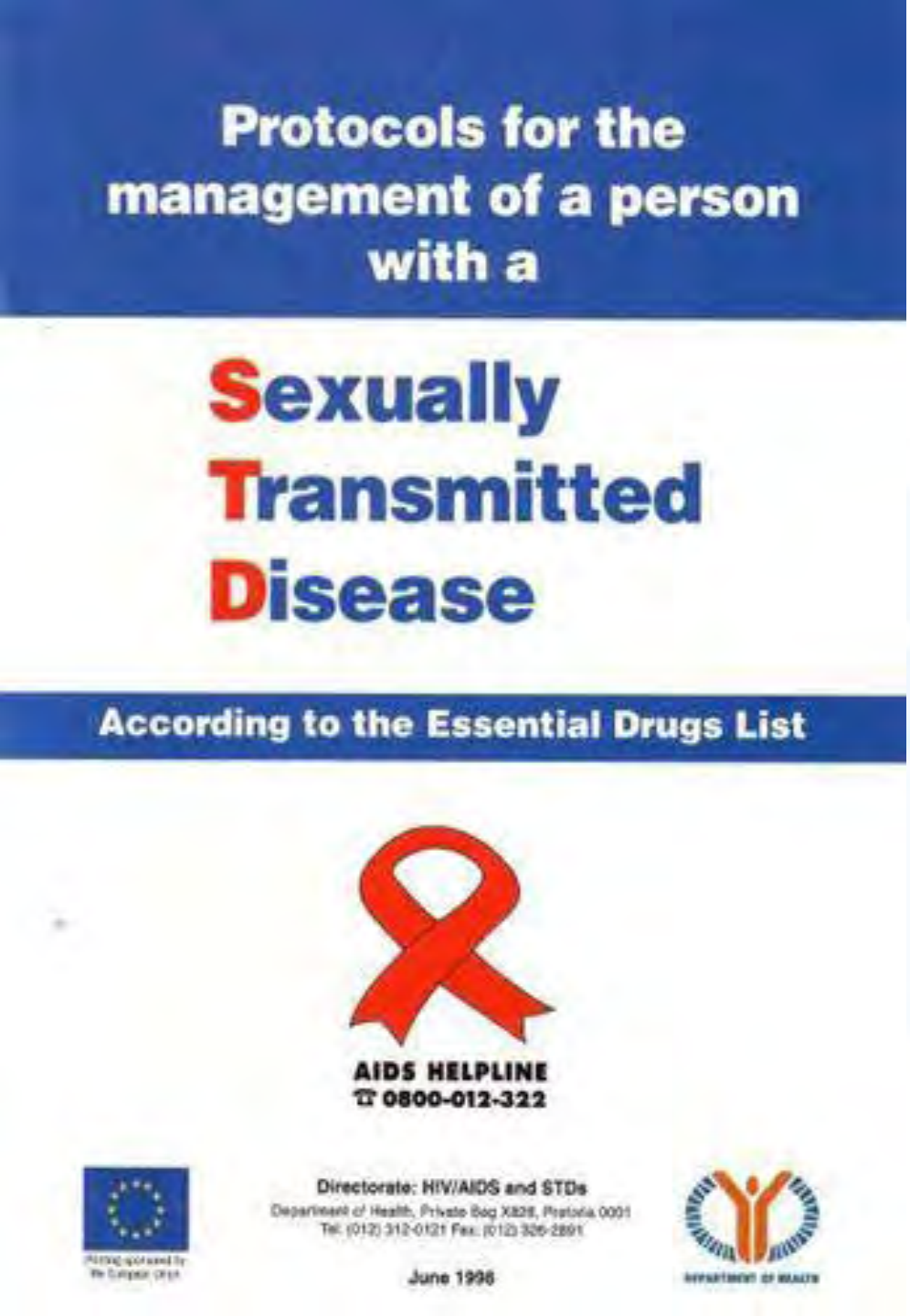
## FUNGUS

- *Candida albicans*

# IMPORTANCE

- Worldwide estimates
  - +/- 340 million curable sexually transmitted infections (STIs)
- Curable STIs - if not treated properly lead to complications
  - Local and disseminated
  - PID
  - Infertility
  - Poor outcome of pregnancy
  - Neonatal morbidity and mortality
- Resource poor settings are reliant on syndromic management
  - Over-treatment and asymptomatics




- **National Department of Health guidelines developed in 1996**
- **Revision 2009** (resistance in GC & emergence of HSV)

# INTERACTION

HIV  STIs

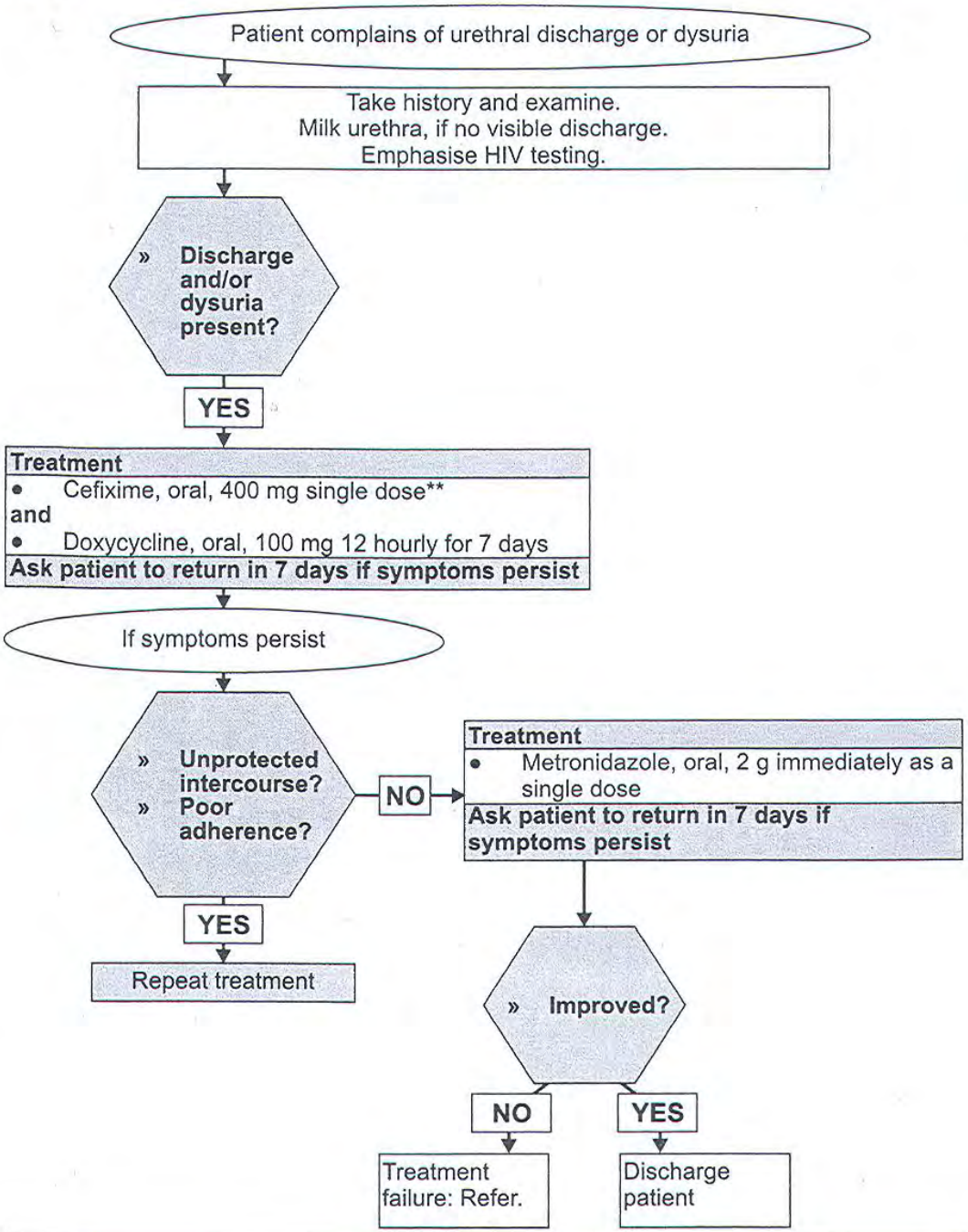
- Enhanced transmission
- Atypical presentation
- Altered serological response
- Change in antimicrobial therapy (agent vs duration)

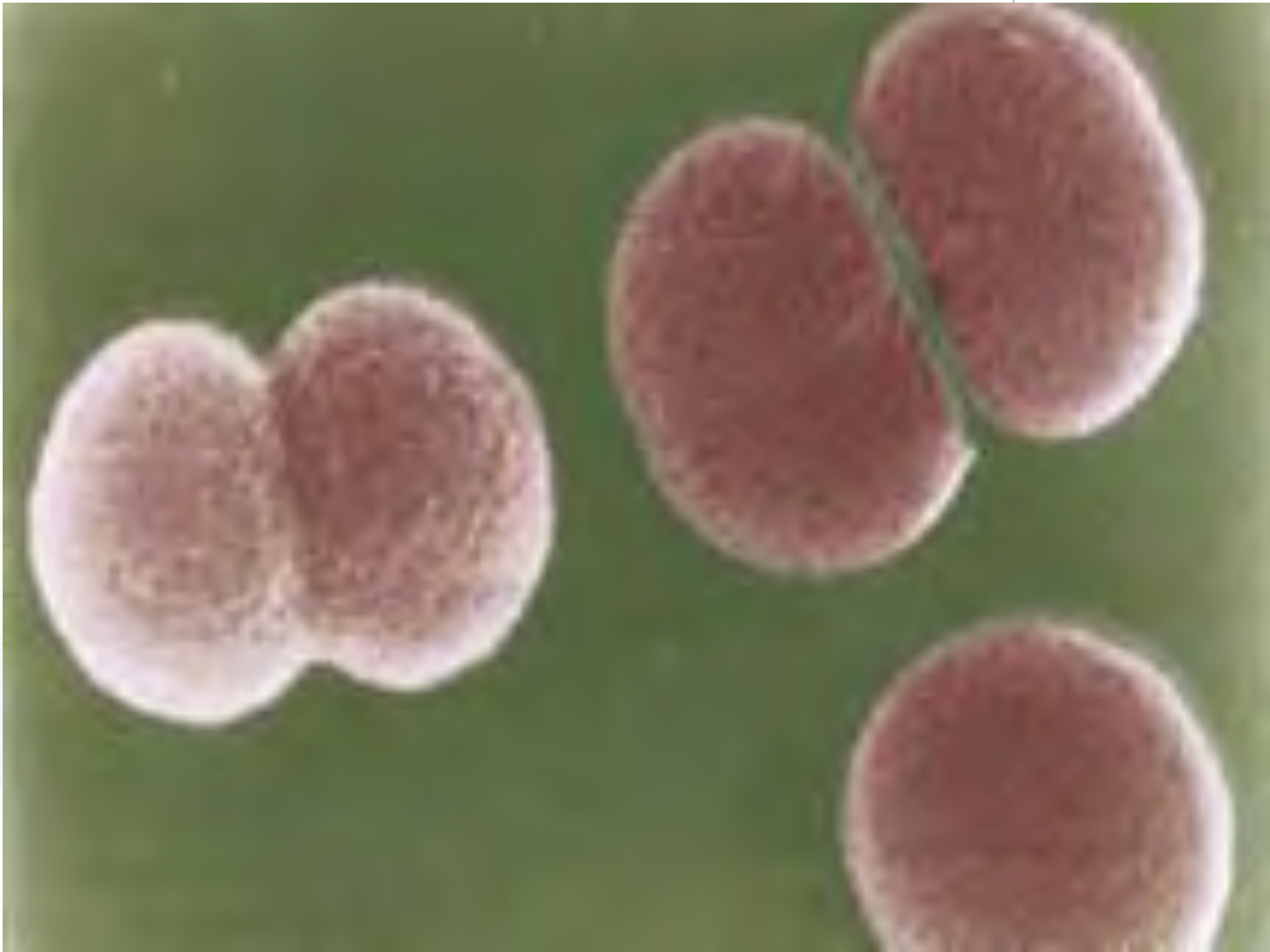
# MALE URETHRAL DISCHARGE

- ***Neisseria gonorrhoeae*……..80 – 95 %**
  - Ceftriaxone, cefixime, spectinomycin
- ***Chlamydia trachomatis*……+/- 40 %**
  - Tetracyclines, macrolides, azithromycin
- ***Trichomonas vaginalis*……..3 – 5 %**
  - Metronidazole; tinidazole
- ***Ureaplasma urealyticum*……...1- 5 %**
  - Tetracycline; azithromycin
- ***Mycoplasma genitalium*……..4 – 16%**
  - Tetracyclines, macrolides, azithromycin

## 12.3 Male urethritis syndrome (MUS)

N34.1





# *Neisseria gonorrhoeae:* PENICILLIN

- Introduced in 1943
- Not used since 1980's/1990's for GC Rx

- **Mechanism of action**
  - Inhibits the formation of peptidoglycan in the bacterial cell wall

- **Resistance**
  - chromosomally- (CMRNG)
  - and/or plasmid-mediated (PPNG).

# *Neisseria gonorrhoeae:* PENICILLIN

- **Low-Level Resistance:**
  - Chromosomally-mediated resistance - low-level
  - Resulting from the additive effects of mutations at several loci, each producing small increments in resistance

  - penA –decreases the affinity of penicillin to bind
  - penB is responsible for reduced permeability of the antibiotic into the cells
  - mtr mediates resistance through an active efflux system

- **High-Level Resistance:**
  - Plasmid-mediated resistance – 1976
  - Plasmids encode a TEM-1 type b−lactamase

  - 2.9 MDa, " Rio"
  - 3.05 MDa "Toronto"
  - 3.2 MDa "African"
  - 3.8 - 4.0 MDa "Nimes"
  - 4.2 - 4.4 MDa "Asian"
  - 6.5 MDa "New Zealand"

# *Neisseria gonorrhoeae:* TETRACYCLINE

**Mechanism of action**

- Tetracycline acts on the process of bacterial translation by inhibiting the incorporation of amino-acyl tRNA into the growing mRNA chain

**Resistance**

- May be chromosomally– and/or plasmid-mediated

**Low-Level Resistance:**

- Chromosomally-mediated resistance to tetracycline occurs when organisms acquire tet genes in its genome or alterations to mtr or penB genes.
- Aggregation of mutations cause the minimum inhibitory concentration (MIC) to increase and cause low-level, yet clinically relevant resistance.

**High-Level Resistance:**

- TRNG (MIC >16.0µg/m) is associated with the tetM determinant, which is plasmid-borne

# *Neisseria gonorrhoeae:* CIPROFLOXACIN

**2nd generation fluoroquinolone**

- Highly successful in for treatment of gonorrhoea
- Preferred because: relatively inexpensive; is an oral agent and is highly effective if the organism is susceptible

**Mechanism of action**

- Inhibit certain bacterial topoisomerase enzymes, especially those that alter the topology of double stranded DNA (dsDNA), namely DNA gyrase and topoisomerase IV

**Low-Level Resistance:**

- Changes in cell permeability as well as efflux mechanisms
- reduce the access of the agent to the target

**High-Level Resistance:**

- High-level, clinically relevant resistance is achieved by altering the target sites via mutations
- Accomplished by mutations in the gyrA and parC genes

# Gonococcal Resistance: Evolving from penicillin, tetracycline to the quinolones in South Africa- implications for treatment guidelines

**Table1: Susceptibility to penicillin (N=141)**

| Category | No. of isolates |
|---|---|
| **PPNG** | 22/141 (16%) |
| **Non-PPNG** | |
| • Fully susceptible | 13/119 (11%) (MIC, ≤ 0.06mg/l) |
| • Decreased susc (MIC, 0.125 –1mg/l) | 87/119 (73%) |
| • CMRNG (≥2mg/l) | 19/119 (16%) |

**Table 3: Susceptibility profile**

**Ciprofloxacin resistance ……7%**

**Ceftriaxone…….....fully susceptible**

**Table 2: Susceptibility to tetracycline (N=141)**

| Category | No. of isolates |
|---|---|
| • Susceptible (MIC, ≤1mg/l) | 65 (46%) |
| • *CMTRNG (MIC, 2 - 8mg/l) | 25 (18%) |
| • **TRNG (MIC, ≥16mg/l) | 51 (36%) |

***Chromosomally mediated tetracycline resistant *N. gonorrhoeae***

**** Plasmid mediated tetracycline resistant *N. gonorrhoeae***



*De Jongh M, Dangor Y, Adam A, Hoosen AA*
*International Journal for STD and AIDS* 2007; 18: 697-99

# *Neisseria gonorrhoeae:* Which agents?

- **Ceftriaxone & cefixime – currently used**

- **Spectinomycin**
  - If parenteral treatment is preferred, spectinomycin seems suitable, although isolates with decreased susceptibility to spectinomycin have been reported
  - Spectinomycin bind to the ribosome and interferes with protein synthesis.

  - **Resistance**
- Resistance to spectinomycin usually occurs via a single-step chromosomal mutation, resulting in high-level resistance