

Sexually Transmitted Infections: An Evidence-Based Online Course

Module 5
Treatment of sexually transmitted infections

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Abbreviations and acronyms

AMR	Antimicrobial resistance
BV	Bacterial vaginosis
CT	Chlamydia trachomatis
GUD	Genital Ulcer Disease
HSV	Herpes simplex virus
LMICs	Low- and Middle-Income Countries
MG	Mycoplasma genitalium
NG	Neisseria gonorrhoeae
STI	Sexually transmitted infection
TP	Treponema pallidum
TV	Trichomonas vaginalis
UDS	Urethral discharge syndrome
VD	Vaginal discharge
VDS	Vaginal discharge syndrome
VVC	Vulvovaginal candidiasis

Module objectives

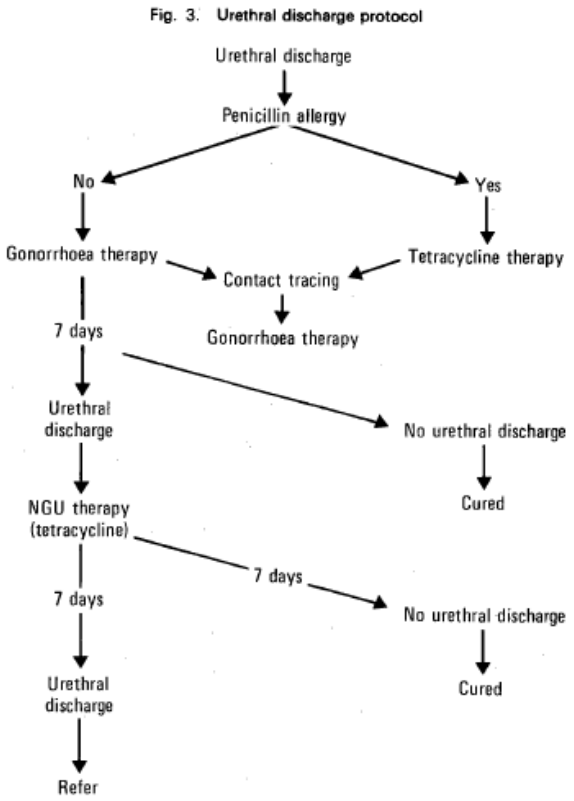
By the end of this module, the learner should be able to:

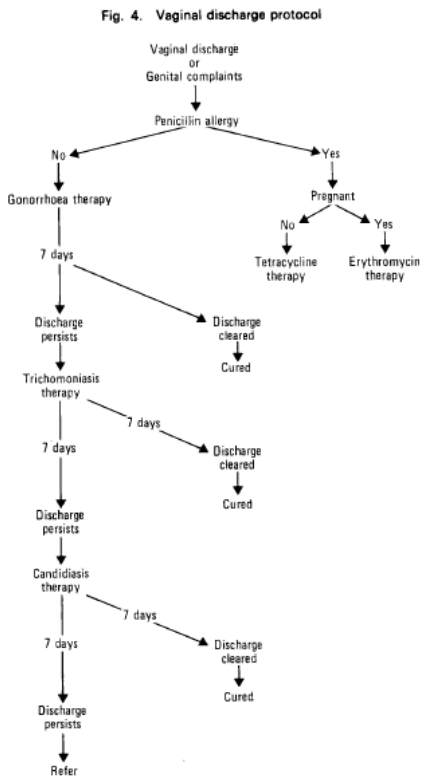
- Describe the pros and cons of syndromic management
- Understand syndromic management approaches to genital discharge
- List the treatment options for pathogens associated with genital discharge
- Understand syndromic management approaches to genital ulcer disease
- List the treatment options for pathogens associated with genital ulcer disease

Module outline

- **Principles of syndromic management**
  - Pros and cons
  - Vaccination
- **Treatment of genital discharge**
  - Syndromic management
  - Aetiologic treatment
- **Treatment of genital ulcer disease**
  - Syndromic management
  - Aetiologic treatment

Introduction to syndromic management





WHO STI treatment algorithms in 1984
Gonorrhoea therapy: IM procaine penicillin G with oral probenecid

- **Evolution of treatment approaches over time**
  - Syndromic –-> diagnostic
  - Evolution of first-line drugs (AMR; user-friendly regimens)
- **Cure rates of syndromic management**
  - UDS: 90-90%
  - VDS: 40-75% (mixed aetiology)
  - GUD: 70-95% (HSV prevalence)
- **Cure rates of STI-specific treatment**
  - Recommended first-line regimens have >90% cure rates incl. CT, NG, TP and TV
  - HSV treatment remains challenging


1984 2003 2021

AMR=Antimicrobial resistance, CT=Chlamydia trachomatis, GUD= Genital Ulcer Disease, HSV=Herpes simplex virus, NG=Neisseria gonorrhoeae, TP=Treponema pallidum, TV=Trichomonas vaginalis, UDS=Urethral discharge syndrome, VDS=Vaginal discharge syndrome

Principles of syndromic management

Syndromic treatment: empirical combination of antibiotics that cover the most likely aetiology of a syndrome without diagnostic testing

Table 3 Advantages and disadvantages of syndromic case management

Criteria	Advantages	Disadvantages
Algorithm	Simple Problem-orientated; based on presenting symptoms	Low sensitivity and specificity for cervical gonococcal and chlamydial infections in women Risk scores are not highly sensitive or specific
Initiation of therapy	Rapid. Patients are treated at first visit without need for laboratory confirmation	Not easily accepted by doctors
Treatment outcome	High rates of cure	Requires surveillance of antibiotic susceptibility profiles Some algorithms do not provide for 2nd or 3rd line treatment
Cost	Saves money on laboratory tests Cost-effective	Leads to overtreatment which may be costly
Coverage	Can achieve high coverage of population	Does not detect asymptomatic cases
Implementation of approach	Can be easily integrated into the PHC system Can rely on nonmedical staff to manage cases	Needs to be adapted to specific settings
Management support systems	Simplifies reporting, supervision and ordering of drugs Facilitates data collection for surveillance and planning	May have to set up a parallel information system in order to monitor trends in traditional aetiological STDs

Three main STI-associated syndromes

1. Vaginal discharge syndrome
2. Urethral discharge syndrome
3. Genital ulcer syndrome

Bosu BK et al. Trop Med Int Health 1999

Linking STI syndrome with bacterial aetiology

TABLE 1: Microbial aetiology of sexually transmitted infection syndromes.

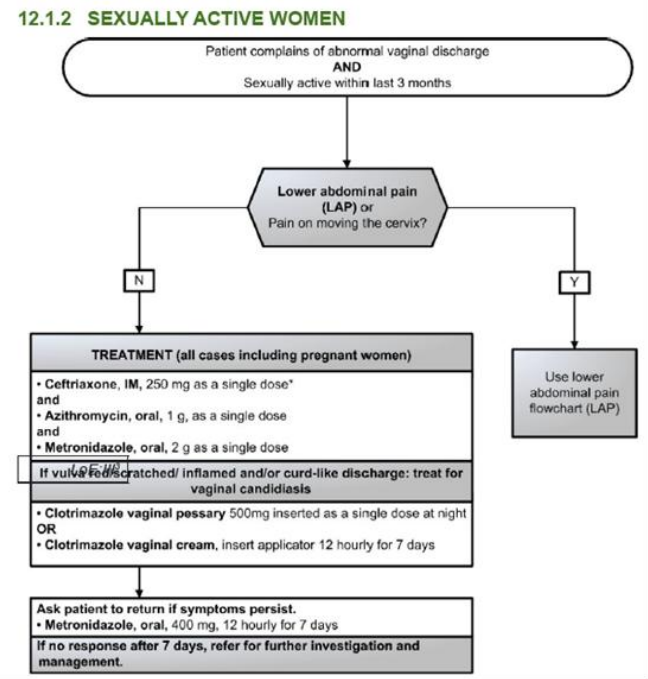
Syndrome	Common aetiology (> 10% of cases)	Less common aetiology (< 10% of cases)
Male urethral discharge syndrome	*Neisseria gonorrhoeae* *Chlamydia trachomatis*	*Mycoplasma genitalium* *Trichomonas vaginalis* Other aetiology
Vaginal discharge syndrome	*Neisseria gonorrhoeae* *Chlamydia trachomatis* *Trichomonas vaginalis* Bacterial vaginosis Candidiasis	*Mycoplasma genitalium* Non-infectious aetiology
Genital ulcer syndrome	HSV-1 and HSV-2 *Treponema pallidum*	*Chlamydia trachomatis* biovar Lymphogranuloma venereum *Haemophilus ducreyi* *Klebsiella granulomatis*

HSV, herpes simplex virus.

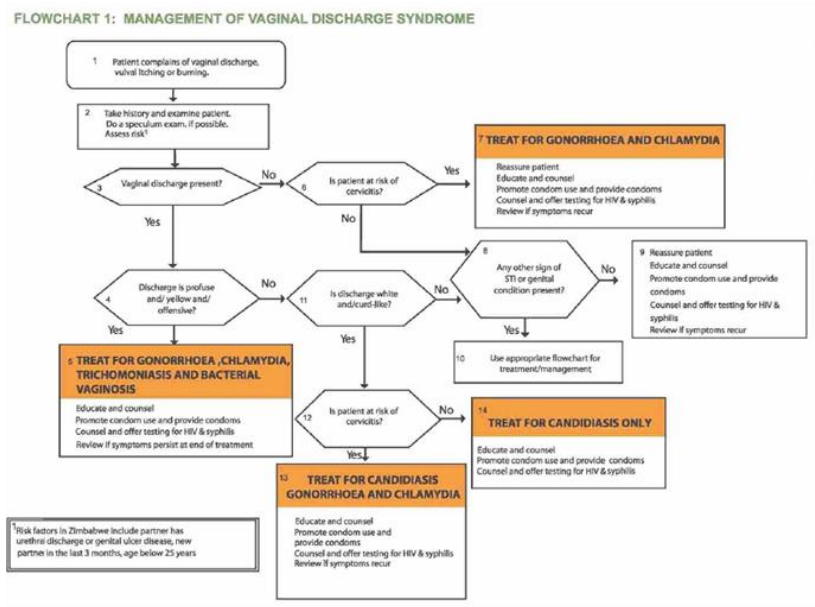
- STI in less than 50% of VDS cases
- >30% of VDS has multiple aetiology

Peters RPH et al. S Afr J HIV Med 2022

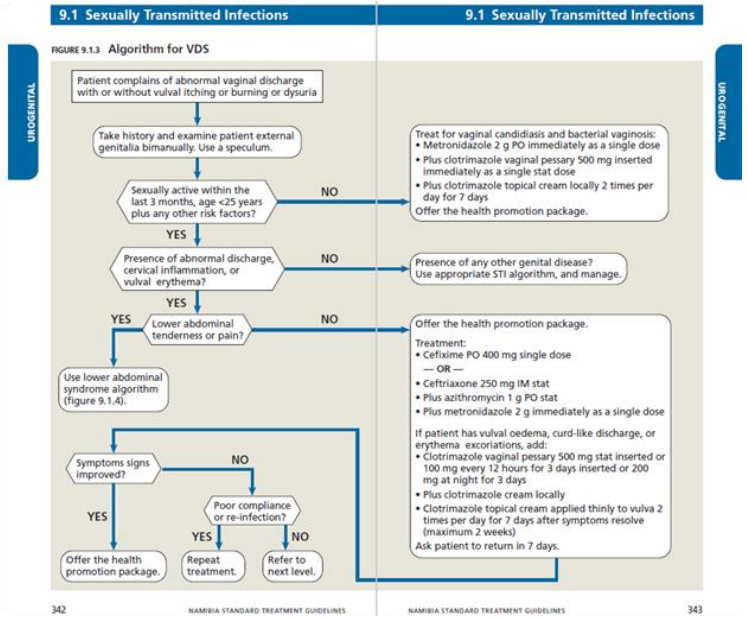
Example of diversity of syndromic management approaches



South Africa

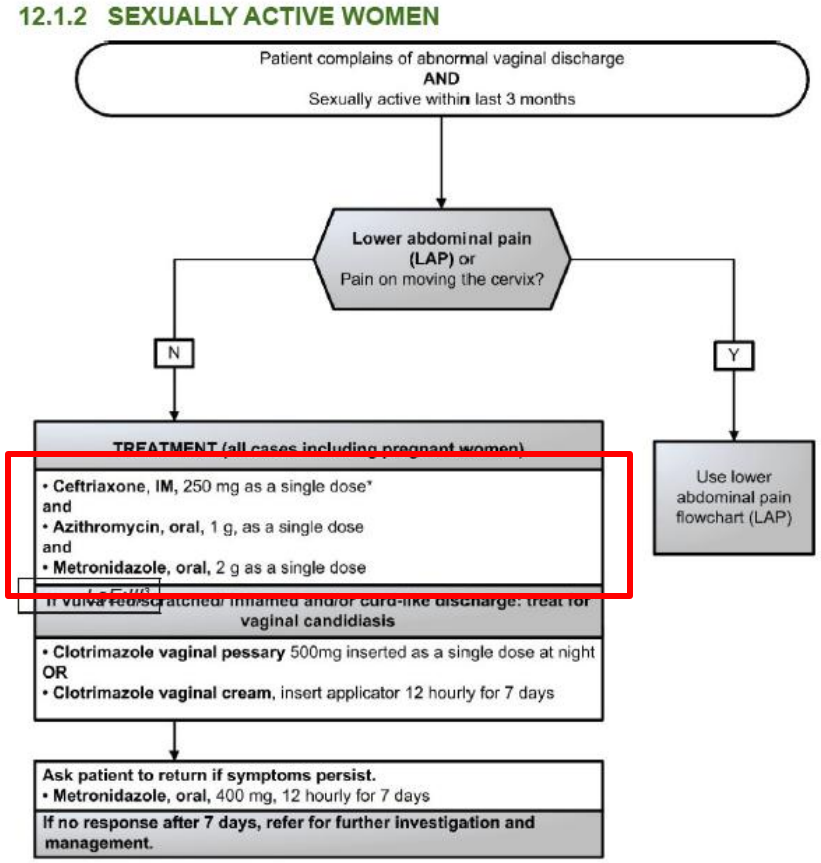


Zimbabwe



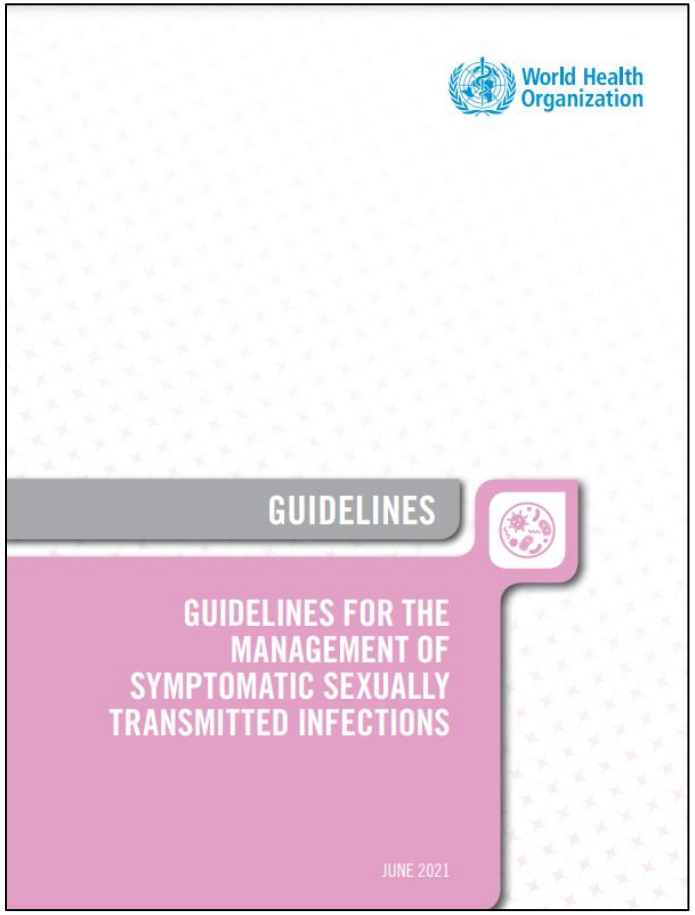
Namibia

Management of VDS: an illustration of overtreatment



- **If 100 women with VDS are managed through the South African algorithm**
  - 15 would have gonorrhoea meaning 85 would receive unnecessary ceftriaxone injection
  - 20 would have chlamydia meaning 80 would receive unnecessary azithromycin
  - Approximately 4/5 women would be overtreated with excessive antibiotics
- **What is the impact and cost of overtreatment and excessive antibiotic use?**

Optimizing syndromic management with diagnostic tests



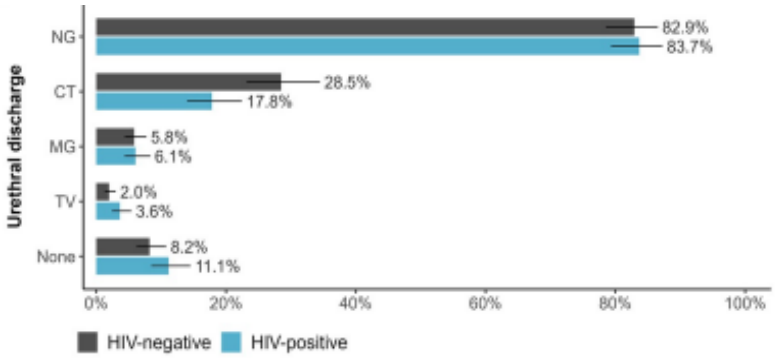
Discharge syndromes

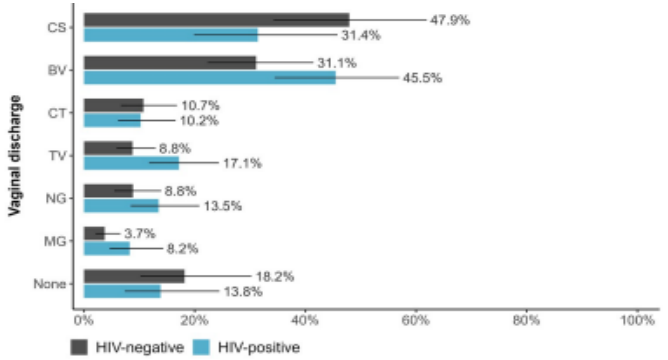
- Urethral discharge
- Vaginal discharge
- Anorectal discharge

Different aetiological profile of genital discharge syndromes

- **Important aetiological differences between UDS and VDS**
  - Gonorrhoea main cause of UDS
  - BV (bacterial vaginosis) and Candida main cause of VDS
  - TV more common in VDS than UDS
  - Mixed aetiology more common in VDS than UDS

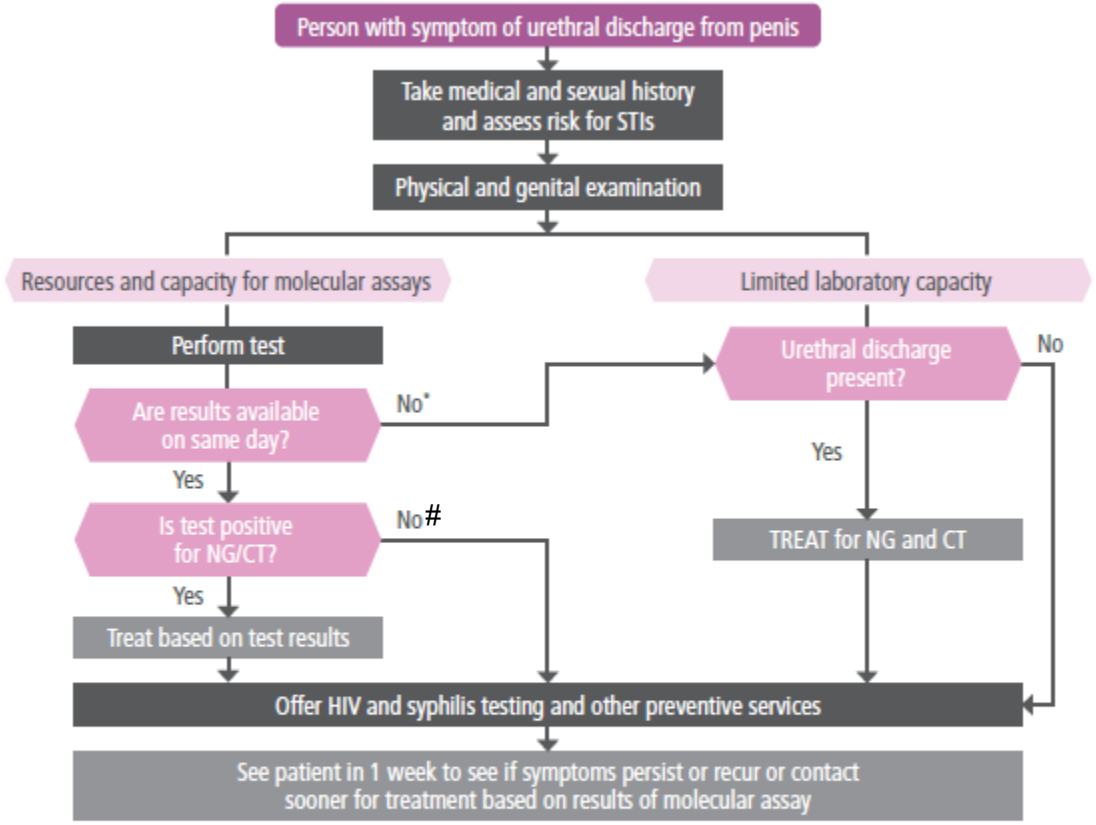
- **Data example: systematic review of discharge aetiology in Southern Africa**





Michalow J et al. PLoS Med 2024

Optimizing management of urethral discharge syndrome



NG, *N.gonorrhoeae*; CT, *C. trachomatis*.

* If molecular assay was performed and results were not available on same day, revise the syndromic treatment initially provided according to the test results when available

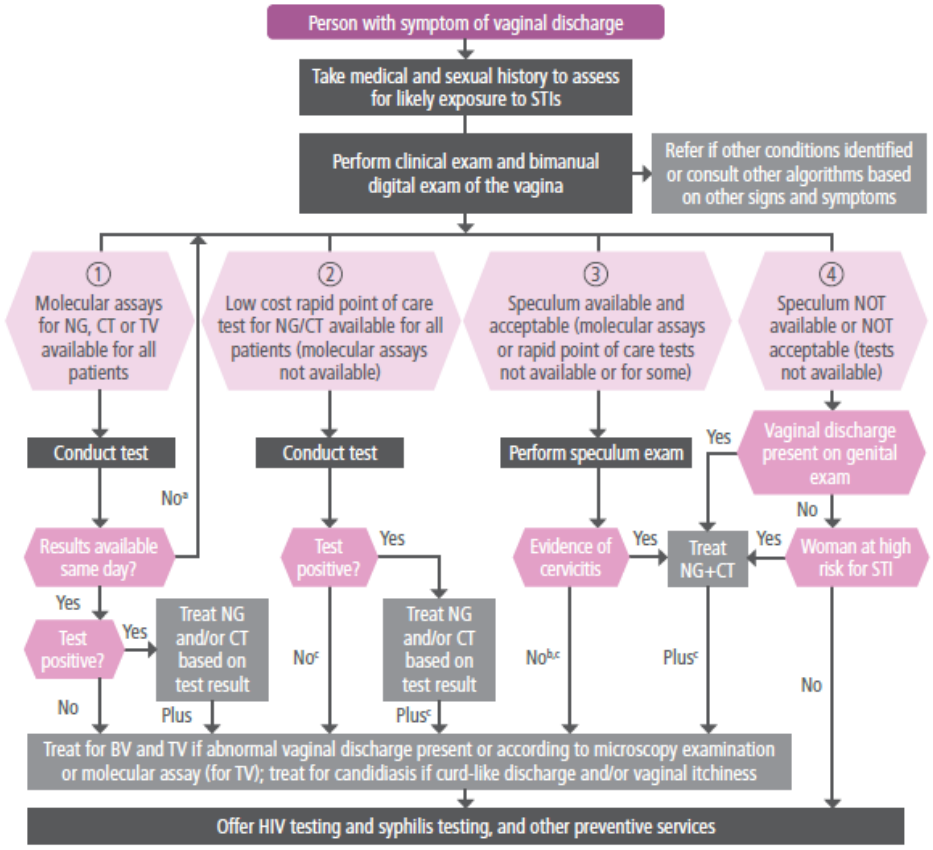
\# If test is negative but urethral discharge is present, treat for non-gonococcal/non-chlamydial urethritis (such as *M. genitalium, T. vaginalis* or herpes simplex virus)

Key points

- Focus on gonorrhoea and chlamydia treatment
- If diagnostic test: importance of same-day results to directly inform treatment decisions
- If no same-day results: adjust syndromic treatment and inform partner management

WHO, 2021

Optimizing management of vaginal discharge syndrome



NG, *N. gonorrhoeae*; CT, *Chlamydia trachomatis*; TV, *Trichomonas vaginalis*; BV, bacterial vaginosis.

[a] If molecular assay was performed and results were not available on same day, revise the syndromic treatment initially provided according to the test results when available

[b] perform rapid point of care test or molecular assay if available to confirm NG/CT and treat if positive; if negative do not treat and ask woman to return if symptoms recur

[c] if woman complains of recurrent or persistent discharge refer to a centre with laboratory capacity

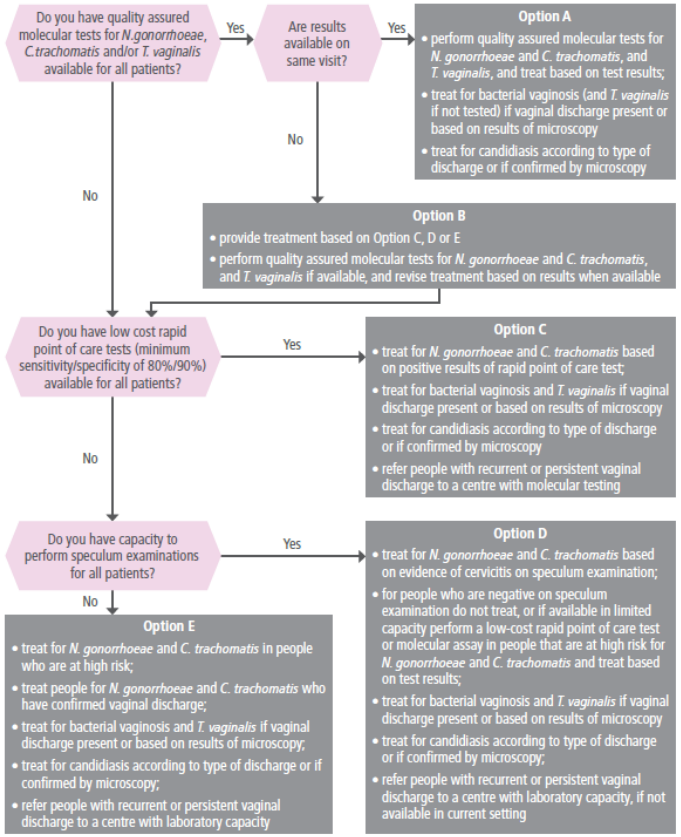
Key points of diagnostic testing

- Focus on diverse aetiology
- If diagnostic test: importance of same-day results of diagnostic test to directly inform treatment decisions
- Relevance if no same-day results: adjust syndromic treatment and inform partner management

WHO, 2021

Optimizing management of vaginal discharge syndrome

Fig. 4. Flow chart for programme managers to determine which management options to implement for vaginal discharge



Four options top optimize syndromic management of VDS

1. Molecular test for CT, NG and TV
2. Low-cost point-of-care test (80%/90%) for NG or CT
3. Syndromic treatment based on speculum evaluation
4. Syndromic treatment

NB. Microscopy may be used to inform TV and/or Candida treatment

WHO, 2021

Syndromic treatment recommendations

Rationale for treatment of urethral discharge

- **Most cases (>90%) caused by *Neisseria gonorrhoeae and/or Chlamydia trachomatis***
  - Ceftriaxone or cefixime to cover gonorrhoea (dose based on local AMR data)
  - Azithromycin or doxycycline to cover chlamydia (single dose vs. slightly higher efficacy)

Rationale for treatment of vaginal discharge

- **VDS has diverse aetiology so broad antimicrobial coverage**
  - Azithromycin or doxycycline to cover *Chlamydia trachomatis* (single dose vs. slightly higher efficacy)
  - Ceftriaxone or cefixime to cover *Neisseria gonorrhoeae* (dose based on local AMR data)
  - Metronidazole single dose or course for *Trichomonas vaginalis* and bacterial vaginosis
  - VVC (Vulvovaginal candidiasis) treatment if pruritus, irritation and thick curdy discharge

STI treatment recommendations

STI	Recommended treatment	Antimicrobial resistance status	Drug development pipeline
Chlamydia trachomatis	Doxycycline Azithromycin	No concern: resistance to first-line drugs not observed	• Limited to preclinical compounds; no new drugs in clinical study phase
Neisseria gonorrhoeae	Ceftriaxone Cefixime	Concerns about increase in cephalosporin resistance	• Gepotidacin (GSK) and zoliflodacin (Innoviva/GARDP) completed phase III non-inferiority trial • Several other drugs in phase I/II trials
Trichomonas vaginalis	Metronidazole Tinidazole	No concern: resistance to 5'nitroimidazoles is low	• Limited to preclinical compounds; no new drugs in clinical study phase
Mycoplasma genitalium	Doxycycline with azithromycin or moxifloxacin	Concerns about macrolide and fluoroquinolone resistance	• Very limited

Therapeutic gap: No combined formulation for syndromic management

Neisseria gonorrhoeae drug resistance

- **Global AMR surveillance**
  - **GLASS**: Global Antimicrobial Resistance and Use Surveillance System
  - **EGASP**: Enhanced Gonococcal Antimicrobial Surveillance Programme

- **Increasing rates of drug resistance globally**
  - Cases of decreased susceptibility or resistance to ceftriaxone reported globally but highest rates in Western Pacific Region
  - Isolates with macrolide resistance observed in almost all countries

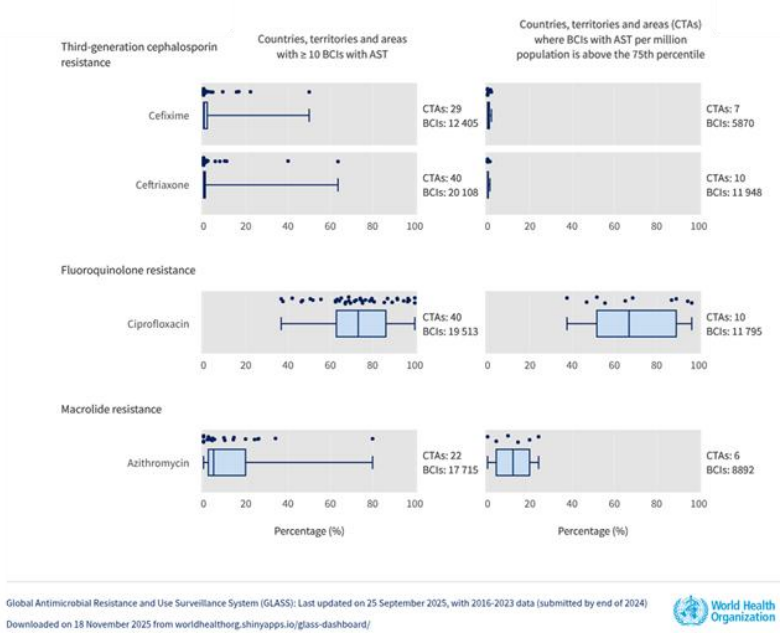
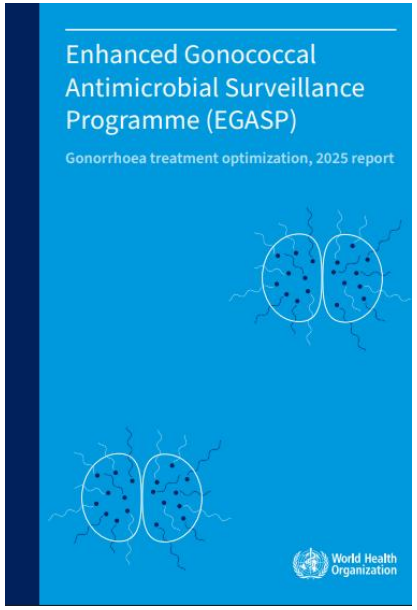
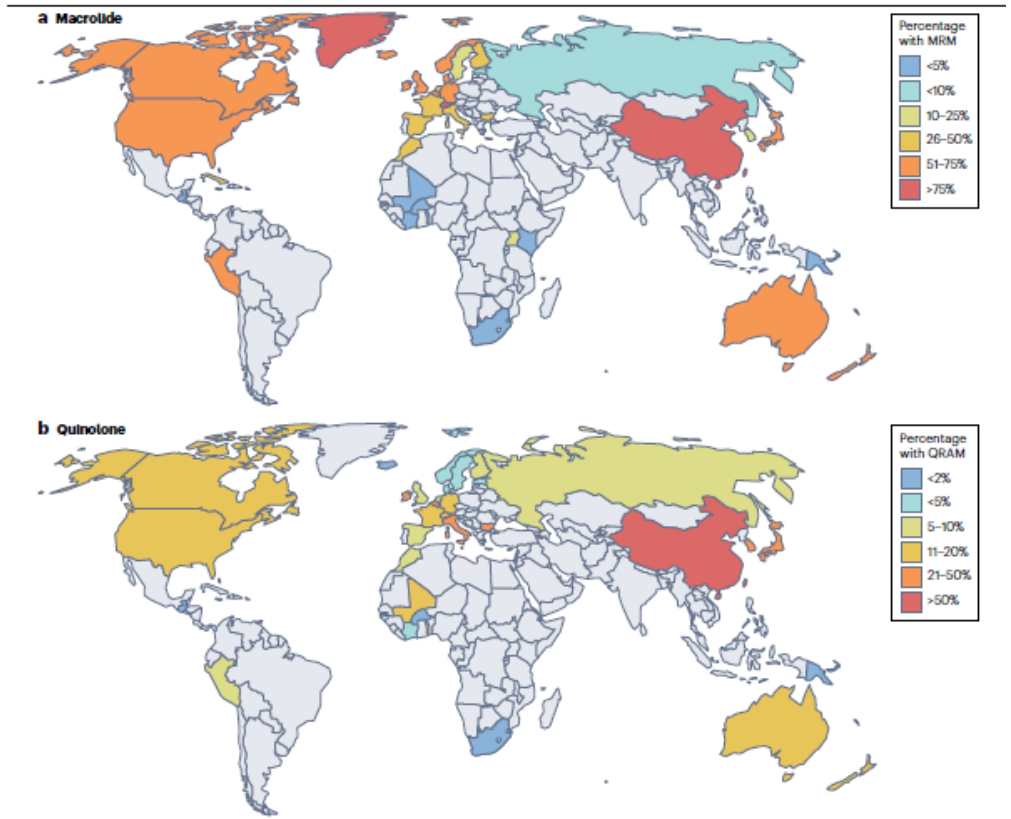


Table 7. Results of antimicrobial resistance testing, EGASP surveillance, 2023

	Cambodia	Indonesia	Malawi	Philippines	South Africa	Thailand	Uganda	Viet Nam	Zimbabwe	Overall
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total Isolates	274	105	122	700	341	373	298	260	18	2491
MIC ceftriaxone										
<0.125 mg/L	232 (85)	105 (100)	122 (100)	696 (100)	341 (100)	373 (100)	298 (100)	207 (80)	18 (100)	2392 (96)
>0.125 mg/L	42 (15)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	53 (20)	0 (0)	95 (4)
MIC cefixime										
<0.125 mg/L	130 (47)	101 (100)	122 (100)	697 (100)	341 (100)	373 (100)	298 (100)	182 (70)	18 (100)	2262 (91)
>0.125 mg/L	144 (53)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	78 (30)	0 (0)	222 (9)
MIC azithromycin										
<1 mg/L	216 (79)	105 (100)	122 (100)	696 (100)	332 (97)	369 (99)	298 (100)	242 (93)	18 (100)	2398 (96)
>1 mg/L (ECOFF)	58 (21)	0 (0)	0 (0)	0 (0)	9 (3)	4 (1)	0 (0)	18 (7)	0 (0)	89 (4)



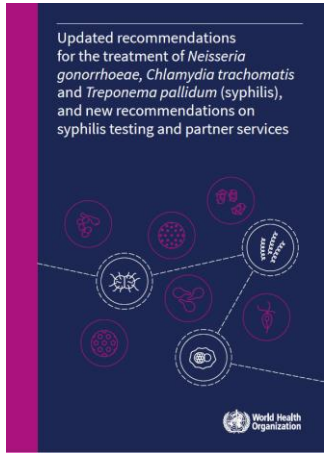
Mycoplasma genitalium drug resistance



- **Global AMR data available from research studies**
  - Uncertainty in resistance estimates due to small sample sizes, selection bias and type of data used
  - Paucity of data from LMICs where syndromic management is used and access to laboratory testing limited
- **Increasing rates of resistance to first-line drugs**
  - Macrolide resistance has been increasing since 2010 when 10% of specimens tested had SNPs (single nucleotide polymorphisms) associated with resistance
  - Increasing rates of fluoroquinolone and dual resistance reported a few years later
  - Higher rates in key populations
- **Impact of dual resistance**
  - Treatment options are few, with suboptimal effectiveness and evidence base is limited

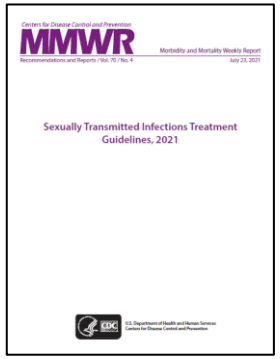
Jensen J & Unemo M. Nat Rev Microbiol 2024
Machalek DA et al. Lancet Infect Dis 2020

WHO STI treatment guidelines 2024 (1)



Infections	First-line options	Effective substitutes
N. gonorrhoeae	Ceftriaxone 1 gram, intramuscularly, single dose	• Cefixime 800 mg, orally, single dose PLUS test of cure OR • Cefixime 800 mg plus Azithromycin 2 grams
C. trachomatis	Doxycycline 100 mg, orally, twice daily for 7 days	• Azithromycin 1 gram, orally, single dose

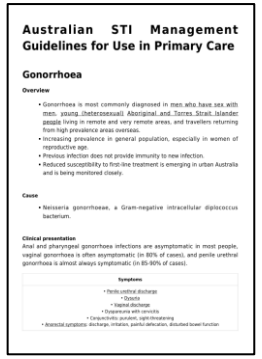
Treatment regimens differ globally based on NG AMR data



USA: 500mg ceftriaxone IM

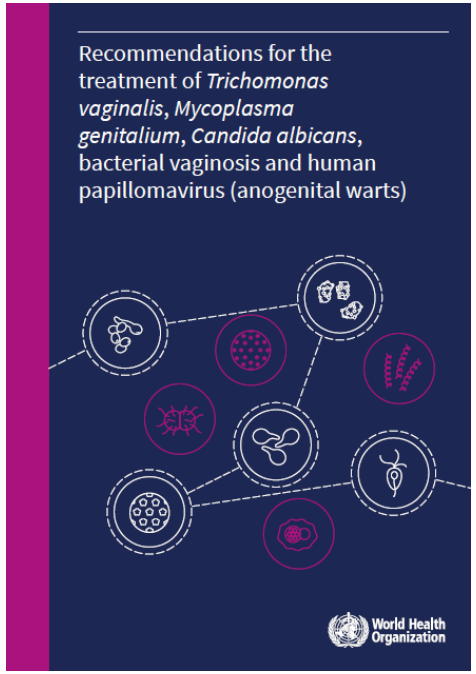


UK: ceftriaxone 1 gram IM



Australia: 500mg ceftriaxone IM plus 1g azithromycin

WHO STI treatment guidelines 2024 (2)



Infections covered	First-line options	Effective substitutes
Bacterial vaginosis	• Metronidazole 400 mg or 500 mg, orally, twice daily for 7 days	Clindamycin , Tinidazole, Secnidazole
Trichomonas vaginalis	• Metronidazole 400 mg or 500 mg, orally, twice daily for 7 days • OR Metronidazole 2 grams, orally, in a single dose	Tinidazole, Ornidazole
***Candida albicans* (yeast infection)**	• Miconazole vaginal pessaries • Clotrimazole vaginal tablet	Fluconazole 150 mg (or 200mg), Nystatin, 200,000-unit vaginal tablet
Mycoplasma genitalium	• Initial treatment: Doxycline 100 mg 2 x a day for 7day - High or suspected high resistance to macrolide or when testing shows resistance to macrolides: Moxifloxacin 400 mg x 7 days - Low or suspected low resistance to macrolides or when testing shows susceptibility to macrolides: Azithromycin 1 g orally once for 1 day then 500 mg once daily for 3 days.	

Patients with recurrent or persistent symptoms

- **Reasons for treatment failure**
  - Lack of partner treatment
  - Sex partner dynamics
  - Suboptimal treatment efficacy
  - AMR still uncommon but on the rise!

- **Recommendation:** treatment decisions based on comprehensive clinical and sexual history

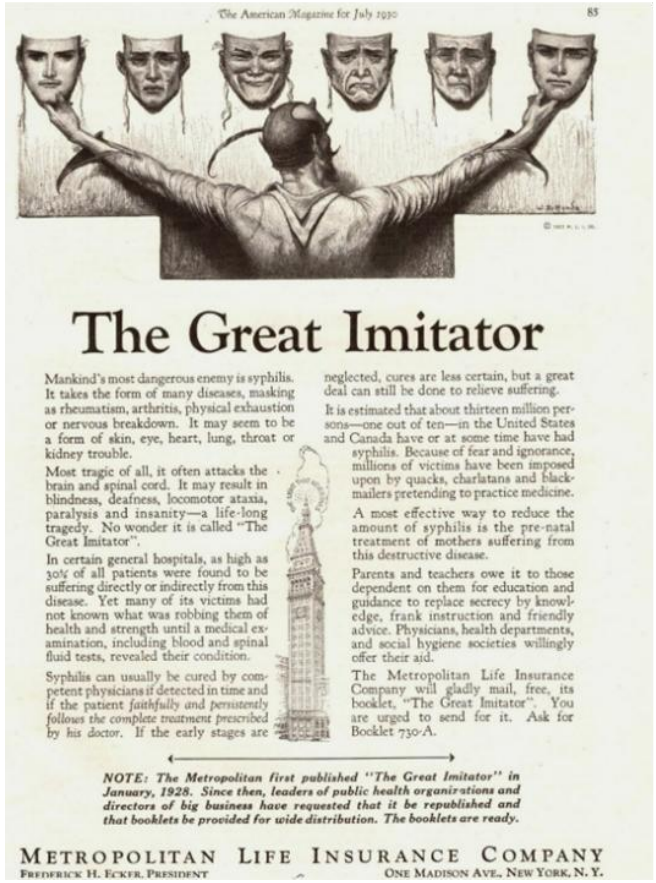
- **Recommendation:** if possible, obtain specimens for diagnostic testing

TABLE 4: Reasons for persistent or recurrent sexually transmitted infection episodes.

Cause	Mechanisms
Sexual partner was not treated	Reinfection by same sex partner
Sexual partner has other partners	New infection with similar or different pathogen
New sexual partner	New infection
Poor treatment compliance	Persistent infection (treatment failure)
Aetiology not covered by initial treatment†	Persistent infection
Treatment with suboptimal efficacy‡	Persistent infection (treatment failure)
Vomiting after treatment	Persistent infection (treatment failure)
Antimicrobial resistance	Treatment failure
Other non-infectious aetiology	No infection

Peters RPH et al. S Afr J HIV Med 2022

How does syphilis typically present?



The American Magazine for July 1930 85

The Great Imitator

Mankind's most dangerous enemy is syphilis. It takes the form of many diseases, masking as rheumatism, arthritis, physical exhaustion or nervous breakdown. It may seem to be a form of skin, eye, heart, lung, throat or kidney trouble.

Most tragic of all, it often attacks the brain and spinal cord. It may result in blindness, deafness, locomotor ataxia, paralysis and insanity—a life-long tragedy. No wonder it is called "The Great Imitator".

In certain general hospitals, as high as 30% of all patients were found to be suffering directly or indirectly from this disease. Yet many of its victims had not known what was robbing them of health and strength until a medical examination, including blood and spinal fluid tests, revealed their condition.

Syphilis can usually be cured by competent physicians if detected in time and if the patient *faithfully and persistently follows the complete treatment prescribed by his doctor.* If the early stages are neglected, cures are less certain, but a great deal can still be done to relieve suffering.

It is estimated that about thirteen million persons—one out of ten—in the United States and Canada have or at some time have had syphilis. Because of fear and ignorance, millions of victims have been imposed upon by quacks, charlatans and blackmailers pretending to practice medicine.

A most effective way to reduce the amount of syphilis is the pre-natal treatment of mothers suffering from this destructive disease.

Parents and teachers owe it to those dependent on them for education and guidance to replace secrecy by knowledge, frank instruction and friendly advice. Physicians, health departments, and social hygiene societies willingly offer their aid.

The Metropolitan Life Insurance Company will gladly mail, free, its booklet, "The Great Imitator". You are urged to send for it. Ask for Booklet 730-A.

NOTE: The Metropolitan first published "The Great Imitator" in January, 1928. Since then, leaders of public health organizations and directors of big business have requested that it be republished and that booklets be provided for wide distribution. The booklets are ready.

METROPOLITAN LIFE INSURANCE COMPANY
FREDERICK H. ECKER, PRESIDENT — ONE MADISON AVE., NEW YORK, N. Y.











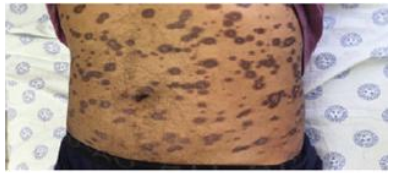


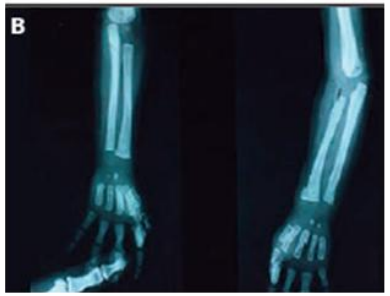








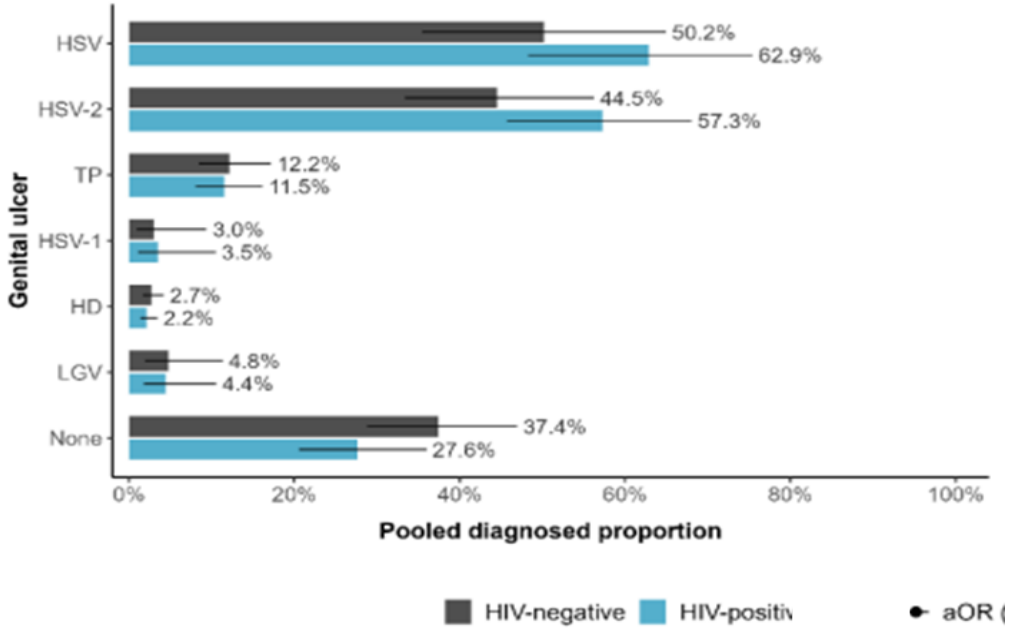






Peeling RW et al. Lancet 2023
Stafford IA et al. New Engl J Med 2024
Peters RPH et al. S Afr J HIV Med 2024

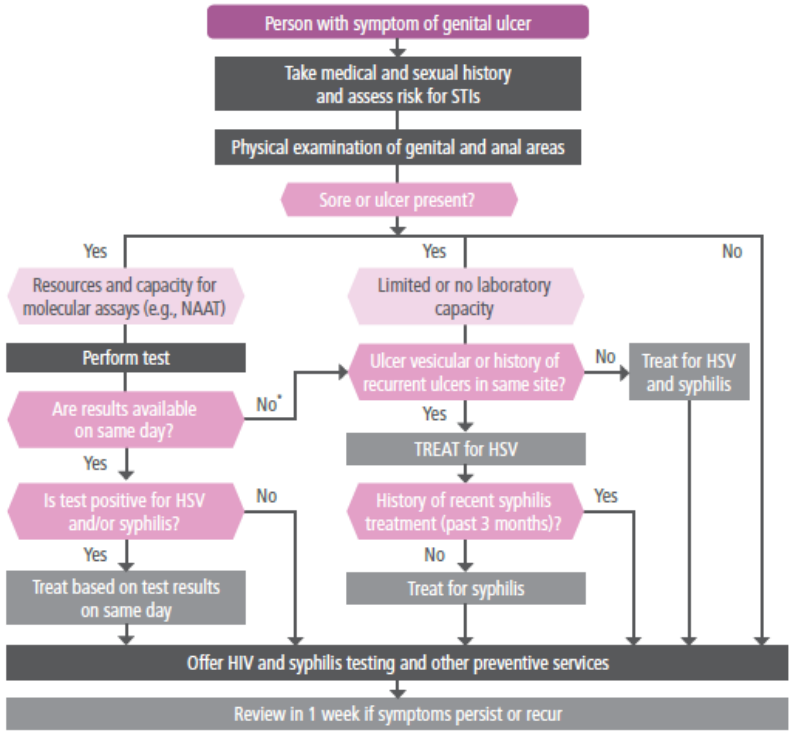
Aetiology of genital ulcer disease in sub-Saharan Africa



- **HSV is dominant cause of GUD** followed by syphilis
- **Mixed HSV/TP infections occur** but in minority of cases
- **Ulcer appearance is not predictive of aetiology**: treatment decisions should not be taken on clinical presentation

Loh AWJ et al. Front Med 2022
Michalow J et al. 2024

Syndromic management of genital ulcer disease



Rationale for treatment of genital ulcer disease

- Generally caused by HSV and/or syphilis; clinical presentation has poor predictive value for aetiology
  - Regimen to cover syphilis in syndromic treatment is the same as used for treatment of early syphilis
  - BPG recommended over doxycycline but dependent on availability
  - Treatment may be limited to acyclovir if adequate recent syphilis treatment, recurrent HSV lesions in same site, or no recent sex partner (<3 months)

Regimens for syndromic and aetiological treatment are the same for early syphilis and HSV

WHO, 2021

BPG is treatment mainstay for syphilis

- **BPG is a long-acting penicillin formulation**
  - Single dose >3 weeks above therapeutic threshold for syphilis (sustained treponemicidal levels)
  - Other penicillin drugs require more frequent dosing which may not be feasible
  - Newborn follow-up essential if non-BPG formulation is used

Formulation	Type	Route	Half-life	Dosing Frequency
Penicillin G (Aqueous)	Short-acting	IV/IM	~0.5 hours	Every 4–6 hours IV
Penicillin V (Phenoxymethylpenicillin)	Short-acting	Oral	~0.5–1 hour	Every 6–8 hours orally
Amoxicillin	Short-acting	Oral	~1–1.5 hours	Every 8–12 hours orally
Procaine Penicillin G	Intermediate	IM	~12–24 hours	Once daily IM
Benzathine Penicillin G (BPG)	Long-acting	IM	~336 hours (~14 days)	Once weekly IM (syphilis)

Syphilis treatment recommendations

	First choice	Effective substitute
Early syphilis (primary; secondary; early latent)	Benzathine penicillin G; 2.4 million units IM single dose	Procaine penicillin 2.3 million units once daily for 10 days OR Doxycycline 100mg twice daily for 14 days*
Late syphilis or syphilis of unknown duration	Benzathine penicillin G; 2.4 million units IM once weekly for 3 weeks	Procaine penicillin 2.3 million units once daily for 10 days OR Doxycycline 100mg twice daily for 30 days*

*Cannot be used in pregnancy. In rare situations, ceftriaxone can be used provided close monitoring.

Macrolides should be avoided given the emergency of resistance in recent years.

Herpes simplex virus treatment recommendations

	First choice	Effective substitute
Primary episode (first episode)	Acyclovir 400mg, orally, three times daily for 10 days OR Acyclovir 200mg, orally, five times daily for 10 days	Valaciclovir 500mg, orally, twice daily for 10 days OR Famciclovir 250mg, orally, three times daily for 10 days
Recurrent episode(s)	Acyclovir 400mg, orally, three times daily for 5 days OR Acyclovir 200mg, orally, five times daily for 5 days	Valaciclovir 500mg, orally, twice daily for 5 days OR Famciclovir 250mg, orally, three times daily for 5 days
Suppressive therapy	Acyclovir 400mg, orally, twice daily	Valaciclovir 500mg, orally, once daily OR Famciclovir 250mg, orally, twice daily

Key messages

- **Syndromic management**
  - Cheap, easy to implement and effective with good cure rates in resource-limited settings
  - Poor antimicrobial stewardship and excessive use of resources
- **Treatment of genital discharge**
  - Different aetiology of urethral discharge and vaginal discharge means different algorithms
  - First-line treatment is a cephalosporin for gonorrhoea and doxycycline or azithromycin for chlamydia
  - Single-dose or course of metronidazole important to cover trichomoniasis and BV in women with discharge
- **Treatment of genital ulcer disease**
  - Predominantly HSV followed by syphilis; chancroid rare
  - Benzathine penicillin G is treatment mainstay with a course of doxycycline as effective substitute
  - HSV treatment with acyclovir based on the frequency of occurrence

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Thank you!