World Health Organization

GUIDELINES FOR THE MANAGEMENT OF SYMPTOMATIC SEXUALLY TRANSMITTED INFECTIONS

WEB ANNEX E. SYSTEMATIC REVIEW FOR SYNDROMIC MANAGEMENT OF GENITAL ULCER DISEASE

JUNE 2021

World Health Organization

GUIDELINES FOR THE MANAGEMENT OF SYMPTOMATIC SEXUALLY TRANSMITTED INFECTIONS

WEB ANNEX E. SYSTEMATIC REVIEW FOR SYNDROMIC MANAGEMENT OF GENITAL ULCER DISEASE

JUNE 2021

Guidelines for the management of symptomatic sexually transmitted infections: Web Annex E. Systematic review for syndromic management of genital ulcer disease

ISBN 978-92-4-003482-2 (electronic version)

Suggested citation. Guidelines for the management of symptomatic sexually transmitted infections: Web Annex E. Systematic review for syndromic management of genital ulcer disease. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

This publication forms part of the WHO guideline entitled *Guidelines for the management of symptomatic sexually transmitted infections*. It is being made publicly available for transparency purposes and information, in accordance with the *WHO handbook for guideline development*, 2nd edition (2014).

Design and layout by 400 Communications.

CONTENTS

1. INTRODUCTION

Sexually transmitted infections (STIs), including human immunodeficiency virus (HIV), continue to present significant health, social, and economic problems in the developing world, leading to considerable morbidity, mortality, and stigma. In under-resourced settings, the lack of adequate laboratory infrastructure and/or high prohibitive costs of diagnostics means that in many settings, STI management relies on syndromic management rather than aetiological diagnosis and management. In these settings, the detection of asymptomatic STIs is largely non-existent. Therefore, synthesizing the latest evidence for the performance of syndromic STI case management would help the World Health Organization (WHO) in their guideline recommendations for syndromic STI management, last updated in 2003.[1]

To evaluate if there is still a role for syndromic STI management or whether STI diagnostics are critical for STI case management, we systematically reviewed the evidence for the performance of syndromic management of STIs. Specifically, we conducted reviews on the diagnostic accuracy and aetiologies of syndromic case management of genital ulcer, anorectal infection and lower abdominal pain. Our specific objectives were to review the flowcharts used for:

- people presenting with genital ulcer disease to detect herpes simplex virus (HSV) or syphilis or lymphogranuloma venereum (LGV) or chancroid, or if no flowcharts found, a minor review of test accuracy of different tests, or risk association/prevalence.
- people presenting with the anorectal syndrome to detect anal STIs or if no flowcharts found, a major review of test accuracy of different tests, or risk association/prevalence.
- people presenting with lower abdominal pain to detect pelvic inflammatory disease (PID) or vaginal or cervical infections, or if no flowcharts found, a major review of test accuracy of different tests, or risk association/prevalence.

2. METHODS

Study inclusion

- Clinical guidelines/algorithms
  - Flow charts for genital ulcer (for syphilis, HSV, LGV, chancroid), anorectal syndromes (for Ct/Ng/Mg/LGV/HSV/Tp/Donovanosis), lower abdominal pain (for PID, vaginal/cervical infections), and vaginal discharge
- Randomized controlled trials
- Observational studies
- Report on at least one of:
  - Comparing syndromic case management against laboratory-confirmed STIs
  - Risk factor analysis of signs/symptoms associated with STI diagnoses and other risk factors associated with STI syndromes

Study exclusion

- Contains no original data i.e. systematic reviews/Letter/editorials/Commentaries/Book chapters
  - But can use these to identify other relevant primary studies
- Qualitative research about outcomes
- Duplicated results from another study
- Laboratory studies about testing STI diagnostic performance
- Studies restricting study population, e.g. men with urethritis, women with cervicitis

Search method

Three separate searches were conducted: one for each of the syndromes under investigation. We included papers that focused on other aspects of syndromic management (i.e. acceptability, feasibility, equity, resources) in addition to the accuracy or sensitivity of the syndromic management approach. The search for each syndrome has been constructed as below.

- Concept 1: syndromic management
- Concept 2: syndrome under investigation
- Concept 3: diagnostic accuracy and sensitivity papers
- Results group 1: concept 1 AND concept 2 AND concept 3
- Results group 2: (concept 1 AND concept 2) NOT Results group 1

A draft search strategy was compiled in the OvidSP Medline database by an experienced information specialist. The search strategy included strings of terms, synonyms and controlled vocabulary terms (where available). As the syndromic management approach was not introduced until 1996, the search was limited to papers published in 1995 or after. No other limits were added. This search strategy was refined with the project team until the results retrieved reflected the scope of the project. The agreed OvidSP Medline search was adapted for each database to incorporate database-specific syntax and controlled vocabularies. Full details of the search strings used for each database can be found in the appendix. A

The following databases were searched on 12 and 13 September 2019.

- Ovid SP Medline and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, 1946 to September 11, 2019
- OvidSP Embase, 1974 to 11 September 2019
- OvidSP Global Health, 1910 to week 35, 2019
- OvidSP Northern Light Life Sciences Conference Abstracts, 2010 to Week 34, 2019
- Ebsco CINAHL Plus, complete database
- Ebsco Africa-Wide Information, complete database
- Clarivate Analytics Web of Science Core Collection, consisting of the following databases:
  - Science Citation Index Expanded (SCI-EXPANDED), 1970 - present
  - Social Sciences Citation Index (SSCI), 1970 - present
  - Arts & Humanities Citation Index (A&HCI), 1975 - present
  - Conference Proceedings Citation Index - Science (CPCI-S), 1990 - present
  - Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH), 1990 - present
  - Emerging Sources Citation Index (ESCI), 2015 – present
- BIREME/PAHO/WHO Virtual Health Library LILACS, complete database

All citations identified by our searches were imported into EndNote X9 software. Duplicates were identified and removed using the method described on the LAS blog.[1]

Data extraction

We followed the guidelines in the Cochrane Handbook 5.1.[2] Three groups of two independent reviewers screened the title and abstracts of unduplicated papers. Discrepancies in screening were resolved by a third reviewer (JO). Each team extracted relevant data from deduplicated full publications. Risk of bias assessment was conducted using the Joanna Briggs Institute Checklist for diagnostic studies.[3]

[1] Falconer, Jane, Removing duplicates from an EndNote library. Library & Archives Service Blog: London School of Hygiene & Tropical Medicine. 2018. [online blog] http://blogs.lshtm.ac.uk/library/2018/12/07/removing-duplicates-from-an-endnote-library/.

Statistical analysis

Diagnostic accuracy cannot be summarized by one measure as sensitivity and specificity are correlated. Therefore, we must choose hierarchical (multilevel) models that use a binomial data structure, i.e. we use a hierarchical logistic regression model in STATA 13.1. After pooling the studies, we report the sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratio. The inverse of the negative likelihood ratio (1/LR-) can be used to compare with the positive likelihood ratio to indicate whether the positive or negative test result has a greater impact on the odds of disease. Likelihood ratios assess the probability or likelihood that the test result obtained would be expected in a person with the condition, compared to the probability or likelihood that the same result would be seen in a person without the condition.

The positive likelihood ratio $LR+ = \frac{sensitivity}{(1-specificity)} = \frac{TP}{(TP+FN)} \div \frac{FP}{(FP+TN)}$ expresses how many times more likely people with the condition are to receive a positive test result compared to those who do not have the condition, while the negative likelihood ratio $LR- = \frac{(1-sensitivity)}{(specificity)} = \frac{FN}{(TP+FN)} \div \frac{TN}{(FP+TN)}$ expresses how likely it is that people with the condition will receive a negative test result compared to those who do not have the condition.

Likelihood ratio	Approximate* change in probability[12]	Effect on posttest Probability of disease[13]
Values between 0 and 1 *decrease* the probability of disease (-LR)		
0.1	–45%	Large decrease
0.2	–30%	Moderate decrease
0.5	–15%	Slight decrease
1	–0%	None
Values greater than 1 *increase* the probability of disease (+LR)		
1	+0%	None
2	+15%	Slight increase
5	+30%	Moderate increase
10	+45%	Large increase

[12] McGee, Steven (1 August 2002). "Simplifying likelihood ratios". Journal of General Internal Medicine. 17 (8): 647–650. doi:10.1046/j.1525-1497.2002.10750.x. ISSN 0884-8734. PMC 1495095. PMID 12213147.

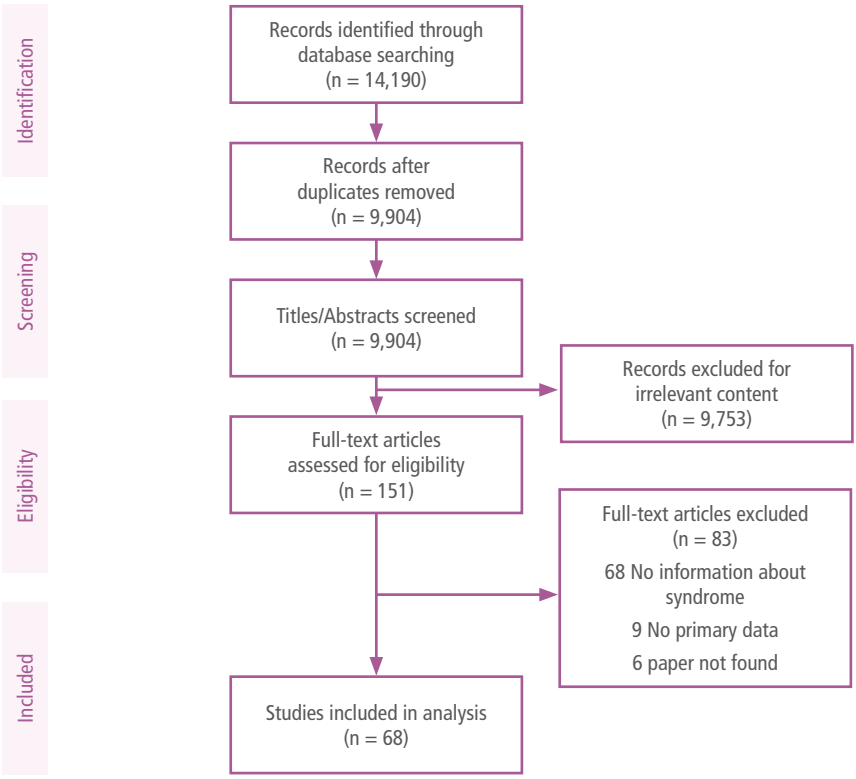
[13] Henderson, Mark C.; Tierney, Lawrence M.; Smetana, Gerald W. (2012). The Patient History (2nd ed.). McGraw-Hill. p. 30. ISBN 978-0-07-162494-7.

To graphically display the trade-off between sensitivity and specificity, we present the summary receiver operating characteristic (SROC) curve from the hierarchical summary receiver operating characteristic (HROC) model [4] and prediction region (i.e. for the forecast of the true sensitivity and specificity in a future study). We also plot the summary operating point and its confidence region. Forest plots for showing within-study estimates and confidence intervals for sensitivity and specificity separately.

In the meta-analyses below, we have only included papers where we could calculate the numbers of true positive, false positives, true negatives and false negatives. For the other papers without this data, we have summarized their results qualitatively (i.e. without pooling).

3. RESULTS

3.1 PRISMA flow chart for genital ulcer syndromes



3.2 Genital ulcer disease

- Country income level
  - 3/68 (4%) High income
  - 23/68 (34%) Upper Middle
  - 25/68 (37%) Lower Middle
  - 15/68 (22%) Low
- Study population recruited from (may not add up to 100% because of multiple recruitment sites)
  - 33/68 (49%) Sexual health clinics
  - 22/68 (32%) Community setting (incl. bar, discos, CBOs)
  - 14/68 (21%) Hospital
- Year of study
  - 54/68 (79%) 2009 and before
  - 9/68 (13%) 2010-2014
  - 5/68 (7%) 2015 and after

For detection of any STIs, four studies provided four estimates for pooling: two studies evaluating the accuracy of GUD to detect any STIs, and two studies evaluating the accuracy of clinical diagnosis of any STIs for a population with GUD. There were too few studies to conduct a meta-analysis.

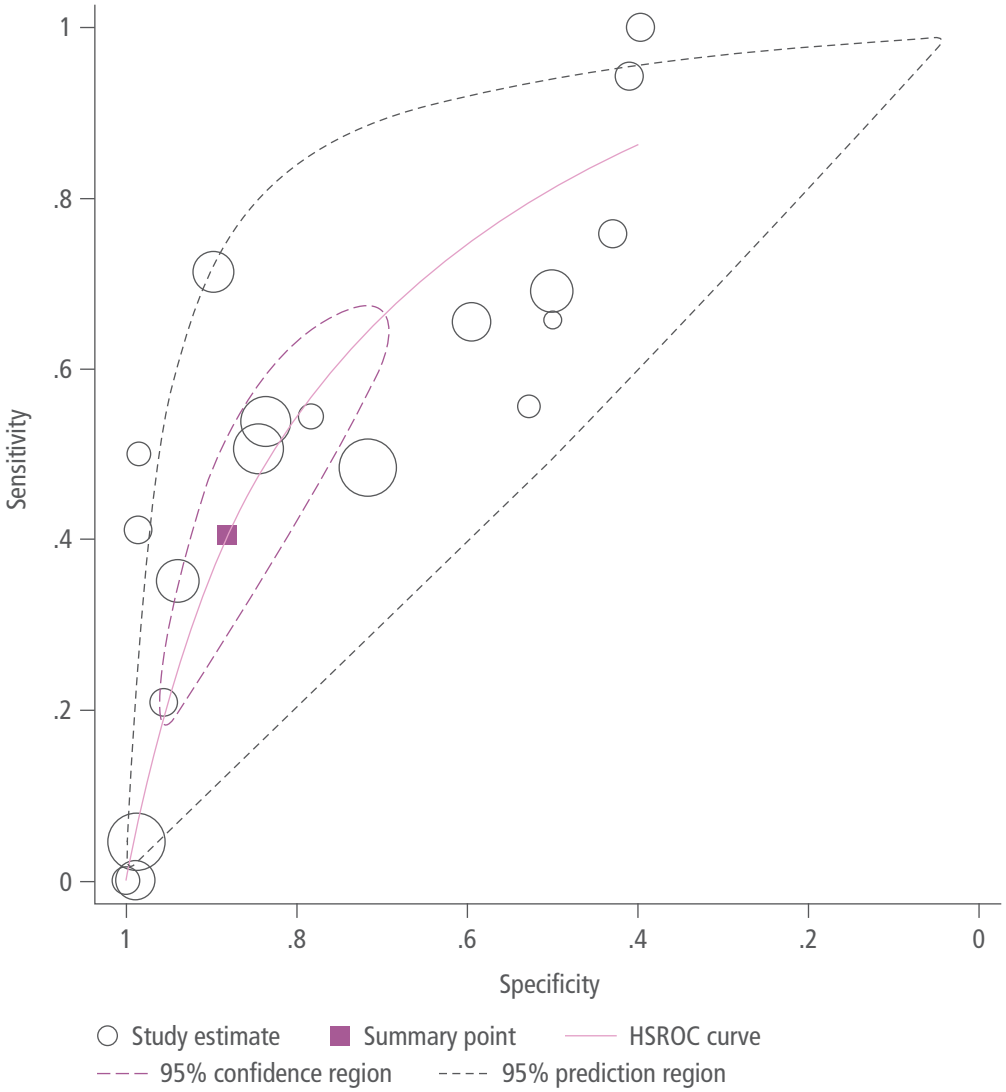
Detection of any STIs for genital ulcer syndrome (shaded rows represents studies testing presence of ulcer to detect any STIs)

Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Pathogens	Diagnostics	True positive	False negative	False positive	True negative
Das[5]	2013	India	Low middle	297	STI and gynaecology outpatients	22% male 12% GUD	Presence of ulcer	HSV, CG, CMV, TP	VDRL, TPHA, Smear, HSV-Ab	14	215	27	41
Liu[6]	2003	China	Upper middle	55	Sexual health clinic	100% male 14% GUD	Presence of ulcer	HSV, TP, HD	PCR, RPR, TPPA	13	0	40	2
Sanchez[7]	1995-6	Dominican Republic	Upper middle	81	General practice	100% male 100% GUD	Symptoms + examination	HSV, TP, HD	M-PCR	13	12	28	28
Sanchez[7]	1995-6	Peru	Upper middle	63	General practice	100% male 100% GUD	Symptoms + examination	HSV, TP, HD	M-PCR	2	7	29	25

For detecting herpes from a clinical diagnosis of herpes, 15 studies provided 20 estimates for pooling. The pooled sensitivity for detecting herpes using a syndromic management approach is 40.4% (95% CI: 23.0-60.6), and pooled specificity is 88.0% (95% CI: 75.3-94.6). The diagnostic odds ratio is 4.95 (95% CI: 3.37-7.28). The positive likelihood ratio is 3.35 (95% CI: 2.27-4.97), and the negative likelihood ratio is 0.68 (95% CI: 0.53-0.86). The inverse negative likelihood ratio is 1.48 (95% CI: 1.16-1.88).

For a cohort of 1000 individuals:

Prevalence	Sensitivity	Specificity	PPV	NPV	Number of cases	Missed cases	False Positive (Overtreated)
0.05	0.404	0.88	0.151	0.966	50	30	114
0.1	0.404	0.88	0.272	0.930	100	60	108
0.15	0.404	0.88	0.373	0.893	150	89	102
0.2	0.404	0.88	0.457	0.855	200	119	96
0.25	0.404	0.88	0.529	0.816	250	149	90
0.3	0.404	0.88	0.591	0.775	300	179	84
0.35	0.404	0.88	0.644	0.733	350	209	78
0.4	0.404	0.88	0.692	0.689	400	238	72
0.45	0.404	0.88	0.734	0.643	450	268	66
0.5	0.404	0.88	0.771	0.596	500	298	60
0.55	0.404	0.88	0.804	0.547	550	328	54
0.6	0.404	0.88	0.835	0.496	600	358	48
0.65	0.404	0.88	0.862	0.443	650	387	42
0.7	0.404	0.88	0.887	0.388	700	417	36
0.75	0.404	0.88	0.910	0.330	750	447	30
0.8	0.404	0.88	0.931	0.270	800	477	24
0.85	0.404	0.88	0.950	0.207	850	507	18
0.9	0.404	0.88	0.968	0.141	900	536	12
0.95	0.404	0.88	0.985	0.072	950	566	6
1	0.404	0.88	1.000	0.000	1000	596	0


1
.8
.6
.4
.2
0
Sensitivity
1
.8
.6
.4
.2
0
Specificity
Study estimate
Summary point
HSROC curve
95% confidence region
95% prediction region

Comparing the accuracy of clinical diagnosis of herpes with the aetiological diagnosis of herpes

Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Diagnostics	True positive	False negative	False positive	True negative
Behets[8]	1997	Madagascar	Low	196	Sexual health clinic	71% male	Clinical diagnosis*	M-PCR	0	19	2	175
Behets[9]	1996	Jamaica	Upper middle	304	Sexual Health clinic	83% male	Clinical diagnosis*	M-PCR	85	73	24	122
Beyrer[10]	1995-6	Thailand	Upper middle	38	Sexual health clinic	79% female sex workers	Clinical diagnosis*	M-PCR	21	11	3	3
Bhavsar [11]	2011-12	India	Low middle	96	Hospital	79% male	Clinical diagnosis*	Tzanck smear IgM for HSV-2	33	0	38	25
Bogaerts [12]	1990-92	Rwanda	Low	395	General practice	63% male	History and examination	Cytopathic effect on Vero cells	4	85	4	302
Bogaerts [12]	1990-92	Rwanda	Low	395	General practice	63% male	History and examination + syphilis serology or darkfield microscopy	Cytopathic effect on Vero cells	4	85	4	302
Bogaerts [12]	1990-92	Rwanda	Low	395	General practice	63% male	Clinical diagnosis*	Cytopathic effect on Vero cells	43	46	87	219
DiCarlo [13]	1990-1992	USA	High	220	Sexual health clinic	100% men	Clinical diagnosis*	Culture	20	37	10	153
Hina[14]	2015-16	India	Low middle	96	Sexual health clinic	75% males	Clinical diagnosis*	Tzanck smears, HSV2-IgM	33	2	36	25
Htun[15]	1993-94	Lesotho	Low middle	92	Sexual health clinic		Clinical diagnosis*	MPCR	7	10	1	74
Htun[15]	1993-94	Lesotho	Low middle	92	Sexual health clinic		Clinical diagnosis*	MPCR	5	19	3	65

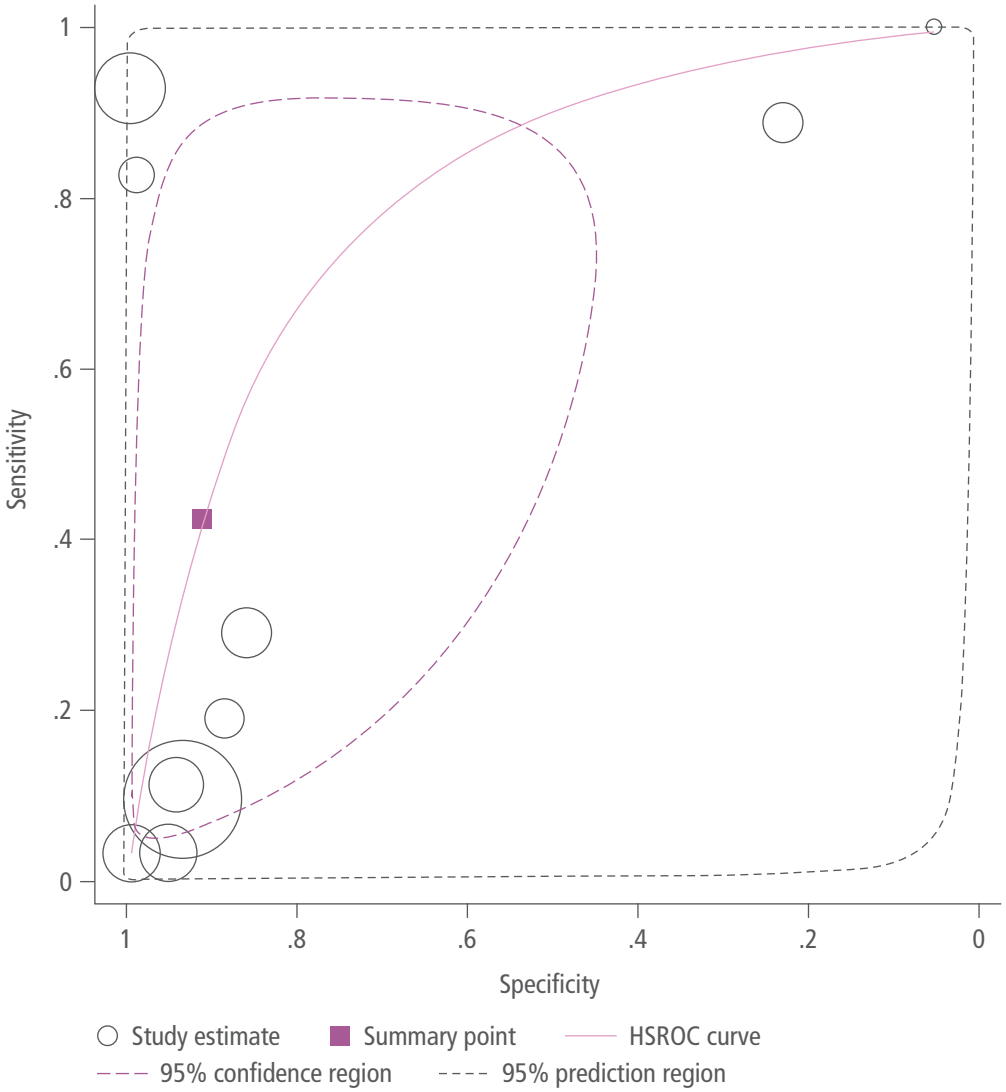
Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Diagnostics	True positive	False negative	False positive	True negative
Htun[15]	1993-94	Lesotho	Low middle	92	Sexual health clinic		Clinical diagnosis*	MPCR	0	24	0	68
Prabhakar [16]	2008-9	India	Low middle	181	Sexual health clinic	100% male	Clinical diagnosis*	M-PCR	59	31	37	54
Risbud[17]	1994	India	Low middle	302	Sexual health clinic		Clinical diagnosis*	M-PCR	48	47	32	175
Sanchez[7]	1995-6	Dominican Republic	Upper middle	81	General practice	100% male	Clinical diagnosis*	M-PCR	19	16	10	36
Sanchez[7]	1995-6	Peru	Upper middle	63	General practice	100% male	Clinical diagnosis*	M-PCR	15	12	17	19
Wang[18]	1998-99	China	Upper middle	96	Sexual health clinic	52% males	Clinical diagnosis*	M-PCR	25	8	36	27
Wang[19]	2000-1	China	Upper middle	227	Sexual health clinic	90% male	Clinical diagnosis*	M-PCR	49	22	78	78
Fast[20]	1980	Kenya	Low middle	70	"Special treatment clinic"	100% male	Clinical diagnosis*	Culture	3	3	1	63
Dangor [21]	Unclear	South Africa	Upper middle	210	Hospital	100% male	Clinical diagnosis*	Culture	5	2	21	182

*"Diagnostic test" is clinician's diagnosis of herpes (rather than the presence of ulcer) – Clinical diagnosis is based on physical examination and history

For detecting herpes from the presence of a genital ulcer, seven studies provided ten estimates for pooling. The pooled sensitivity for detecting herpes using a syndromic management approach is 42.2% (95% CI: 10.9-81.3), and pooled specificity is 91.0% (95% CI: 65.9-98.1). The diagnostic odds ratio is 7.38 (95% CI: 1.29-42.09). The positive likelihood ratio is 4.69 (95% CI: 1.22-18.01), and the negative likelihood ratio is 0.64 (95% CI: 0.32-1.27). The inverse negative likelihood ratio is 1.57 (95% CI: 0.79-3.15).

For a cohort of 1000 individuals:

Prevalence	Sensitivity	Specificity	PPV	NPV	Number of cases	Missed cases	False Positive (Overtreated)
0.05	0.422	0.91	0.198	0.968	50	29	86
0.1	0.422	0.91	0.343	0.934	100	58	81
0.15	0.422	0.91	0.453	0.899	150	87	77
0.2	0.422	0.91	0.540	0.863	200	116	72
0.25	0.422	0.91	0.610	0.825	250	145	68
0.3	0.422	0.91	0.668	0.786	300	173	63
0.35	0.422	0.91	0.716	0.745	350	202	59
0.4	0.422	0.91	0.758	0.703	400	231	54
0.45	0.422	0.91	0.793	0.658	450	260	50
0.5	0.422	0.91	0.824	0.612	500	289	45
0.55	0.422	0.91	0.851	0.563	550	318	41
0.6	0.422	0.91	0.876	0.512	600	347	36
0.65	0.422	0.91	0.897	0.459	650	376	32
0.7	0.422	0.91	0.916	0.403	700	405	27
0.75	0.422	0.91	0.934	0.344	750	434	23
0.8	0.422	0.91	0.949	0.282	800	462	18
0.85	0.422	0.91	0.964	0.217	850	491	14
0.9	0.422	0.91	0.977	0.149	900	520	9
0.95	0.422	0.91	0.989	0.077	950	549	4
1	0.422	0.91	1.000	0.000	1000	578	0


1
.8
.6
.4
.2
0
Sensitivity
1
.8
.6
.4
.2
0
Specificity
Study estimate
Summary point
HSROC curve
95% confidence region
95% prediction region

Comparing the accuracy of the presence of GUD with the aetiological diagnosis of herpes

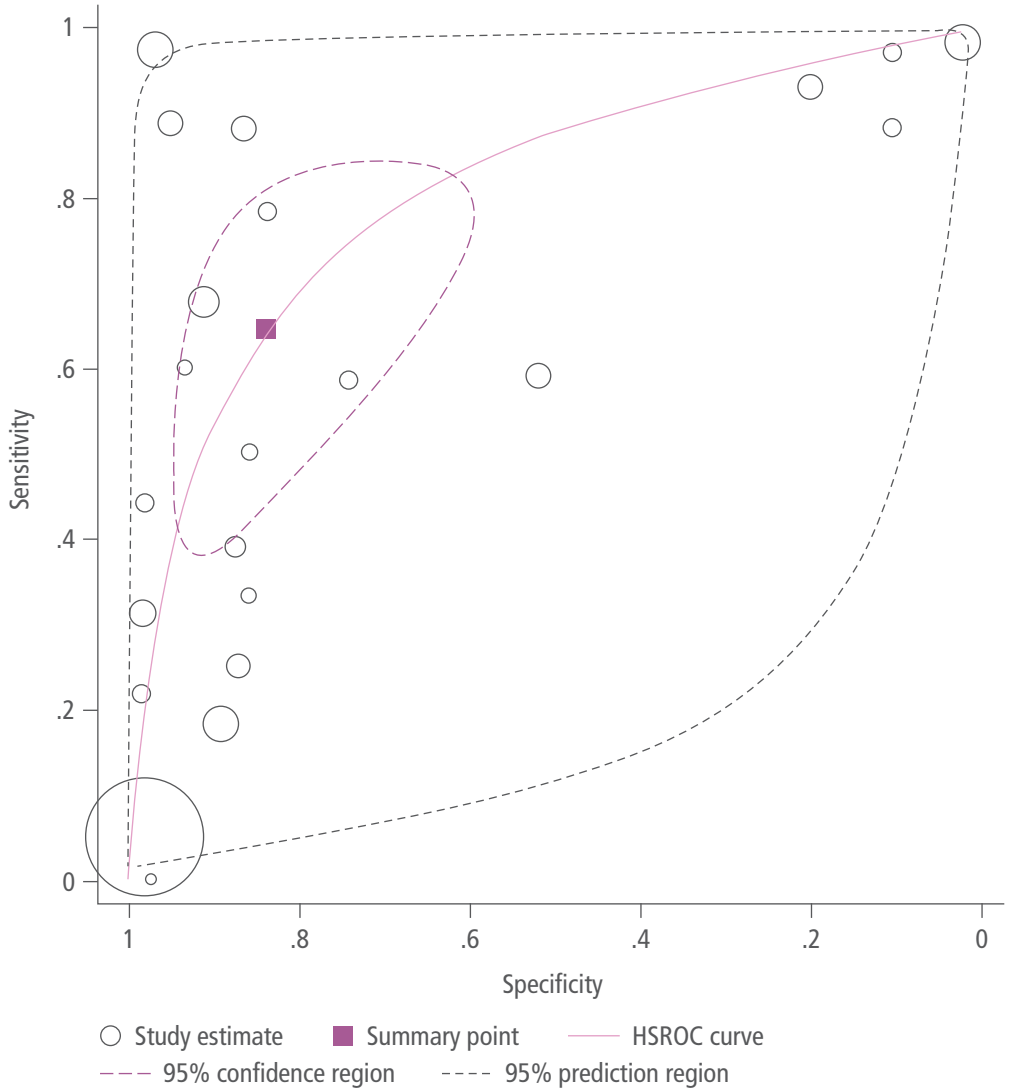
Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Diagnostics	True positive	False negative	False positive	True negative
Choudhry [22]	2007-8	India	Low middle	300	Sexual health clinic	64% male 16% MSM	Clinical diagnosis*	Gram stain, HSV-IgM	57	12	3	228
Clark[23]	2003-5	Peru	Upper middle	3285	Community setting	73% heterosexual men 16% MSM	Clinical diagnosis*	HSV2-Ab	78	770	162	2275
Liu[6]	2003	China	Upper middle	55	Sexual health clinic	67% male 7.5% GUD	Presence of ulcer	PCR	15	0	38	2
Muralidhar [24]	2013	India	Low middle	1208	Sexual health clinic	100% heterosexuals 25.4% GUD	Clinical diagnosis*	Giemsa stain, PCR, HSV2-IgM	76	6	5	1121
O'Farrell [25]	2007	South Africa	Upper middle	642	Sexual health clinic	50% males 7% GUD	Symptoms + risk factors	HSV2-Ab	140	347	22	133
Otieno[26]	2007-9	Kenya	Low middle	786	Enrolled in general population study	100% females living with HIV	Clinical diagnosis*	HSV2-IgG	0	14	14	796
Shah[27]	2008	El Salvador	Low middle	366	Hospital	100% males living with HIV	Self-reported symptoms	HSV-2 serology	61	262	5	38
Shah[27]	2008	El Salvador	Low middle	366	Hospital	FSW	Self-reported symptoms	HSV-2 serology	55	7	234	69
Shah[27]	2008	El Salvador	Low middle	366	Hospital	MSM	Self-reported symptoms	HSV-2 serology	20	647	234	69
Shah[27]	2008	El Salvador	Low middle	366	Hospital		Self-reported symptoms	HSV-2 serology	37	299	22	345

*Clinical diagnosis is based on physical examination and history

To detect syphilis using a clinical diagnosis of syphilis among individuals with GUD, 15 studies provided 22 estimates for pooling. The pooled sensitivity for detecting syphilis is 64.4% (95% CI: 44.8-80.2), and pooled specificity is 83.7% (95% CI: 67.0-92.9). The diagnostic odds ratio is 9.32 (95% CI: 4.35-20.00). The positive likelihood ratio is 3.96 (95% CI: 2.08-7.54), and the negative likelihood ratio is 0.42 (95% CI: 0.27-0.66). The inverse of the negative likelihood ratio is 2.35 (95% CI: 1.52-3.65).

For a cohort of 1000 individuals:

Prevalence	Sensitivity	Specificity	PPV	NPV	Number of cases	Missed cases	False Positive (Overtreated)
0.05	0.644	0.837	0.172	0.978	50	18	155
0.1	0.644	0.837	0.305	0.955	100	36	147
0.15	0.644	0.837	0.411	0.930	150	53	139
0.2	0.644	0.837	0.497	0.904	200	71	130
0.25	0.644	0.837	0.568	0.876	250	89	122
0.3	0.644	0.837	0.629	0.846	300	107	114
0.35	0.644	0.837	0.680	0.814	350	125	106
0.4	0.644	0.837	0.725	0.779	400	142	98
0.45	0.644	0.837	0.764	0.742	450	160	90
0.5	0.644	0.837	0.798	0.702	500	178	82
0.55	0.644	0.837	0.828	0.658	550	196	73
0.6	0.644	0.837	0.856	0.611	600	214	65
0.65	0.644	0.837	0.880	0.559	650	231	57
0.7	0.644	0.837	0.902	0.502	700	249	49
0.75	0.644	0.837	0.922	0.439	750	267	41
0.8	0.644	0.837	0.940	0.370	800	285	33
0.85	0.644	0.837	0.957	0.293	850	303	24
0.9	0.644	0.837	0.973	0.207	900	320	16
0.95	0.644	0.837	0.987	0.110	950	338	8
1	0.644	0.837	1.000	0.000	1000	356	0


1
.8
.6
.4
.2
0
Sensitivity
1
.8
.6
.4
.2
0
Specificity
Study estimate
Summary point
HSROC curve
95% confidence region
95% prediction region

Comparing the accuracy of clinical diagnosis of herpes with the aetiological diagnosis of herpes

Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Diagnostics	True positive	False negative	False positive	True negative
Behets[8]	1997	Madagascar	Low	196	Sexual health clinic	71% male	Clinical diagnosis*	M-PCR	52	4	112	28
Behets[9]	1996	Jamaica	Upper middle	304	Sexual Health clinic	83% male	Clinical diagnosis*	M-PCR	21	10	24	249
Beyrer[10]	1995-6	Thailand	Upper middle	38	Sexual health clinic	79% female sex workers	Clinical diagnosis*	M-PCR	0	1	1	36
Bhavsar [11]	2011-12	India	Low middle	96	Hospital	79% male	Clinical diagnosis*	VDRL, TPHA	19	24	1	52
Bogaerts [12]	1990-92	Rwanda	Low	395	General practice	63% male	History and examination	RPR, TPHA, Darkfield microscopy	108	2	279	6
Bogaerts [12]	1990-92	Rwanda	Low	395	General practice	63% male	History and examination + syphilis serology or darkfield microscopy	RPR, TPHA, Darkfield microscopy	107	3	9	276
Bogaerts [12]	1990-92	Rwanda	Low	395	General practice	63% male	Clinical diagnosis*	RPR, TPHA, Darkfield microscopy	20	90	31	254
DiCarlo [13]	1990-1992	USA	High	220	Sexual health clinic	100% men	Clinical diagnosis*	Darkfield microscopy	14	31	3	172
Hanson [28]	1996	Zambia	Low middle	95	Hospital	100% male	Clinical diagnosis*	Darkfield microscopy, RPR, TPHA	24	17	14	40
Hanson [28]	1996	Zambia	Low middle	131	Hospital	100% female	Clinical diagnosis*	Darkfield microscopy, RPR, TPHA	14	22	12	83

Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Diagnostics	True positive	False negative	False positive	True negative
Htun[15]	1993-94	Lesotho	Low middle	92	Sexual health clinic		Clinical diagnosis*	MPCR, RPR, FTA-Abs	5	18	1	68
Htun[15]	1993-94	Lesotho	Low middle	92	Sexual health clinic		Clinical diagnosis*	MPCR, RPR, FTA-Abs	30	4	52	6
Htun[15]	1993-94	Lesotho	Low middle	92	Sexual health clinic		Clinical diagnosis*	MPCR, RPR, FTA-Abs	33	1	52	6
Ndinya-Achola[29]	1990-91	Kenya	Low middle	172	Primary care	47% males	Clinical diagnosis*	RPR	6	18	19	129
Prabhakar [16]	2008-9	India	Low middle	181	Sexual health clinic	100% male	Clinical diagnosis*	M-PCR	26	18	72	78
Sanchez[7]	1995-6	Dominican Republic	Upper middle	81	General practice	100% male	Clinical diagnosis*	M-PCR	2	2	11	66
Sanchez[7]	1995-6	Dominican Republic	Upper middle	63	General practice	100% male	Clinical diagnosis*	M-PCR	2	4	8	49
Wang[18]	1998-99	China	Upper middle	96	Sexual health clinic	100% had "STI symptoms"	Clinical diagnosis*	M-PCR, RPR, TPPA	18	5	12	61
Wang[19]	2000-1	China	Upper middle	227	Sexual health clinic	90% male	Symptoms + Examination + Risk factors	M-PCR, Darkfield microscopy, RPR, TPPA	94	12	6	115
Fast[20]	1980	Kenya	Low middle	70	"Special treatment clinic"	100% male	Clinical diagnosis*	RPR, Darkfield microscopy	6	4	4	56
Dangor [21]	Unclear	South Africa	Upper middle	210	Hospital	100% male	Clinical diagnosis*	RPR, FTA-ABS, darkfield microscopy	22	3	25	160

*Clinical diagnosis is based on physical examination and history

For detection of syphilis from the presence of GUD, 12 studies provided 15 estimates for pooling. The pooled sensitivity for detecting syphilis is 20.0% (95% CI: 7.0-45.3), and pooled specificity is 92.6% (95% CI: 81.6-97.2). The diagnostic odds ratio is 3.12 (95% CI: 1.24-7.88). The positive likelihood ratio is 2.70 (95% CI: 1.23-5.91), and the negative likelihood ratio is 0.86 (95% CI: 0.71-1.05). The inverse of the negative likelihood ratio is 1.16 (95% CI: 0.95-1.41).

For a cohort of 1000 individuals:

Prevalence	Sensitivity	Specificity	PPV	NPV	Number of cases	Missed cases	False Positive (Overtreated)
0.05	0.2	0.926	0.125	0.957	50	40	70
0.1	0.2	0.926	0.231	0.912	100	80	67
0.15	0.2	0.926	0.323	0.868	150	120	63
0.2	0.2	0.926	0.403	0.822	200	160	59
0.25	0.2	0.926	0.474	0.776	250	200	56
0.3	0.2	0.926	0.537	0.730	300	240	52
0.35	0.2	0.926	0.593	0.683	350	280	48
0.4	0.2	0.926	0.643	0.635	400	320	44
0.45	0.2	0.926	0.689	0.586	450	360	41
0.5	0.2	0.926	0.730	0.537	500	400	37
0.55	0.2	0.926	0.768	0.486	550	440	33
0.6	0.2	0.926	0.802	0.436	600	480	30
0.65	0.2	0.926	0.834	0.384	650	520	26
0.7	0.2	0.926	0.863	0.332	700	560	22
0.75	0.2	0.926	0.890	0.278	750	600	19
0.8	0.2	0.926	0.915	0.224	800	640	15
0.85	0.2	0.926	0.939	0.170	850	680	11
0.9	0.2	0.926	0.961	0.114	900	720	7
0.95	0.2	0.926	0.981	0.057	950	760	4
1	0.2	0.926	1.000	0.000	1000	800	0

Diagnosis of syphilis from the presence of GUD

Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Diagnostics	True positive	False negative	False positive	True negative
Choudhry [22]	2007-8	India	Low middle	300	Sexual health clinic	64% male 16% MSM	Clinical diagnosis*	VDRL, TPHA	11	3	4	282
Clark[23]	2003-5	Peru	Upper middle	3285	Community setting	73% heterosexual men 16% MSM	Symptom/ Examination + RPR	RPR, TPPA	6	91	234	2954
Daly[30]	1989-91	Kenya	Low middle	4367	Family planning clinic	100% females	Clinical diagnosis*	RPR	4	79	76	4208
Desai[31]	2000	India	Low middle	118	Sexual health clinic	100% FSW	Symptoms + Examination	RPR, TPHA	4	23	3	88
Liu[6]	2003	China	Upper middle	55	Sexual health clinic	100% male 14% GUD	Presence of ulcer	PCR, RPR, TPPA	13	0	40	2
Muralidhar [24]	2013	India	Low middle	90	Sexual health clinic	67% male 7.5% GUD	Clinical diagnosis*	Darkfield microscopy, PCR, VDRL, TPHA, FTA-Abs	4	3	2	81
Shah[27]	2008	El Salvador	Low middle	366	Hospital	100% females living with HIV	Self-reported symptoms	RPR, TPPA	0	2	4	360

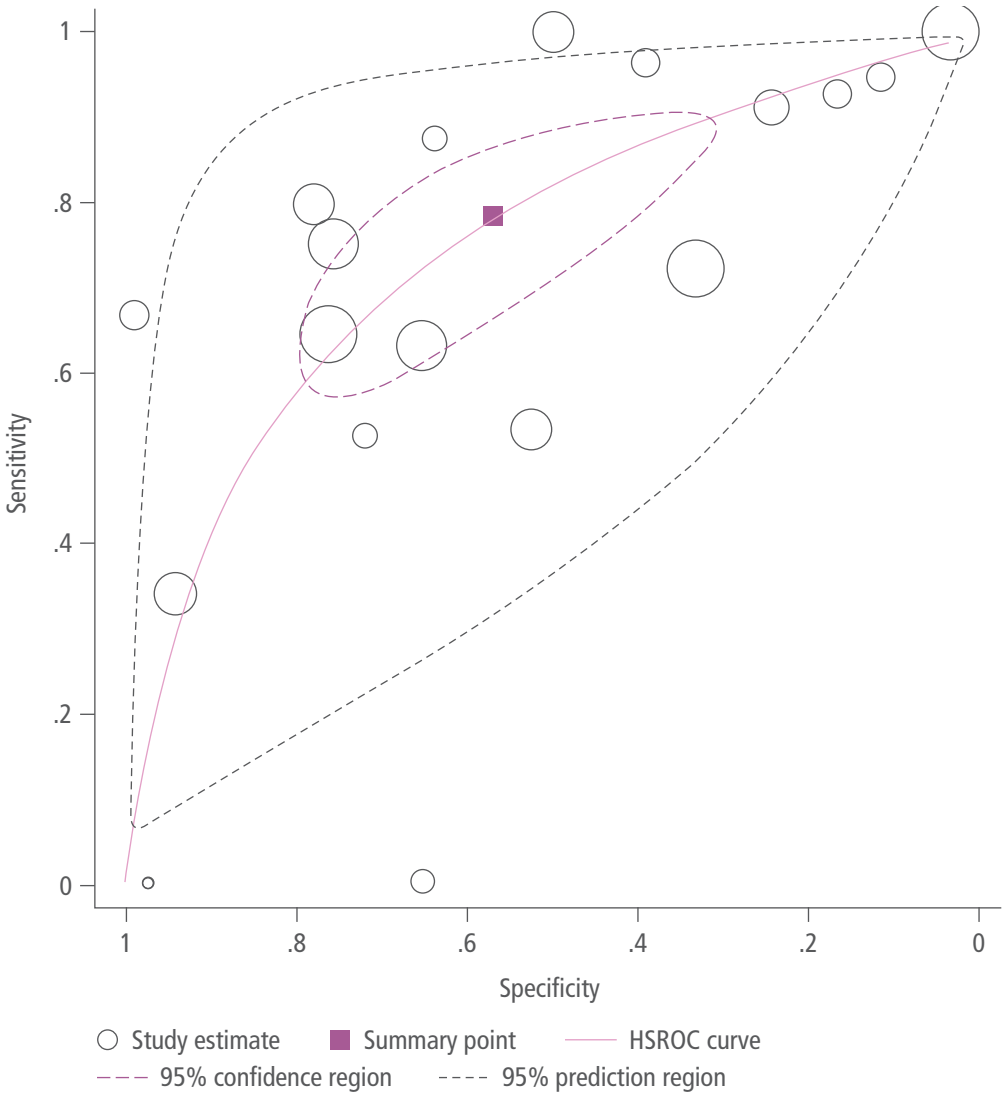
Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Diagnostics	True positive	False negative	False positive	True negative
Shah[27]	2008	El Salvador	Low middle	365	Hospital	100% males living with HIV	Self-reported symptoms	RPR, TPPA	5	58	15	287
Shah[27]	2008	El Salvador	Low middle	768	Hospital	FSW	Self-reported symptoms	RPR, TPPA	1	16	24	727
Shah[27]	2008	El Salvador	Low middle	703	Hospital	MSM	Self-reported symptoms	RPR, TPPA	2	31	65	605
Shahesmaeili [32]	2015	Iran (Islamic Republic of)	Upper middle	1337	Community	100% FSW 3% GUD	Self-reported symptoms	Rapid tests – SD Bioline HIV/Syphilis Duo + Alere Syphilis RPR, EIA	0	5	40	1292
Tsai[33]	2008	Taiwan, China	High	138	Sexual health clinic	100% males 29% GUD	Clinical diagnosis*	RPR, TPHA	26	7	86	19
O'Farrell[25]	2007	South Africa	Upper middle	645	Sexual health clinic	100% heterosexuals 25.4% GUD	Symptoms + risk factors	RPR, TPPA	17	29	147	452
Otieno[26]	2007-9	Kenya	Low middle	824	Enrolled in general population study	50% males 7% GUD	Clinical diagnosis*	RPR, TPPA	0	14	14	796
Yu[34]	2002-4	Taiwan, China	High	307	Sexual health clinic	100% male 11% GUD	Clinical diagnosis	M-PCR, RPR, TPHA	8	13	17	269

*Clinical diagnosis is based on physical examination and history

For detection of chancroid, 13 studies provided 18 estimates for pooling. The pooled sensitivity for detecting chancroid using a syndromic management approach is 78.2% (95% CI: 63.5-88.0), and pooled specificity is 56.5% (95% CI: 37.1-74.2). The diagnostic odds ratio is 4.66 (95% CI: 2.84-7.64). The positive likelihood ratio is 1.80 (95% CI: 1.28-2.52), and the negative likelihood ratio is 0.39 (95% CI: 0.27-0.55). The inverse negative likelihood ratio is 2.59 (95% CI: 1.81-3.71).

For a cohort of 1000 individuals:

Prevalence	Sensitivity	Specificity	PPV	NPV	Number of cases	Missed cases	False Positive (Overtreated)
0.05	0.782	0.565	0.086	0.980	50	11	413
0.1	0.782	0.565	0.166	0.959	100	22	392
0.15	0.782	0.565	0.241	0.936	150	33	370
0.2	0.782	0.565	0.310	0.912	200	44	348
0.25	0.782	0.565	0.375	0.886	250	55	326
0.3	0.782	0.565	0.435	0.858	300	65	305
0.35	0.782	0.565	0.492	0.828	350	76	283
0.4	0.782	0.565	0.545	0.795	400	87	261
0.45	0.782	0.565	0.595	0.760	450	98	239
0.5	0.782	0.565	0.643	0.722	500	109	218
0.55	0.782	0.565	0.687	0.680	550	120	196
0.6	0.782	0.565	0.729	0.633	600	131	174
0.65	0.782	0.565	0.770	0.583	650	142	152
0.7	0.782	0.565	0.807	0.526	700	153	131
0.75	0.782	0.565	0.844	0.463	750	164	109
0.8	0.782	0.565	0.878	0.393	800	174	87
0.85	0.782	0.565	0.911	0.314	850	185	65
0.9	0.782	0.565	0.942	0.224	900	196	43
0.95	0.782	0.565	0.972	0.120	950	207	22
1	0.782	0.565	1.000	0.000	1000	218	0


1
.8
.6
.4
.2
0
Sensitivity
1
.8
.6
.4
.2
0
Specificity
Study estimate
Summary point
HSROC curve
95% confidence region
95% prediction region

Detection of chancroid using a clinical diagnosis of chancroid in a population with GUD

Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Diagnostics	True positive	False negative	False positive	True negative
Behets[8]	1997	Madagascar	Low	196	Sexual health clinic	71% male 100% GUD	Clinical diagnosis*	M-PCR	34	30	63	69
Behets[9]	1996	Jamaica	Upper middle	304	Sexual Health clinic	83% male 100% GUD	Clinical diagnosis*	M-PCR	54	18	57	175
Behets[10]	1995-6	Thailand	Upper middle	38	Sexual health clinic	79% female sex workers 100% GUD	Clinical diagnosis*	M-PCR	0	0	6	32
Bhavsar[11]	2011-12	India	Low middle	96	Hospital	79% male 100% GUD	Clinical diagnosis*	Gram stain	2	1	1	92
Bogaerts[12]	1990-92	Rwanda	Low	395	General practice	63% male 100% GUD	History and examination	Culture	115	0	272	8
Bogaerts[12]	1990-92	Rwanda	Low	395	General practice	63% male 100% GUD	History and examination + syphilis serology or darkfield microscopy	Culture	83	32	188	92
Bogaerts[12]	1990-92	Rwanda	Low	395	General practice	63% male 100% GUD	Clinical diagnosis*	Culture	74	41	67	213
DiCarlo[13]	1990-1992	USA	High	220	Sexual health clinic	100% men 100% GUD	Clinical diagnosis*	Culture	40	78	6	96
Htun[15]	1993-94	Lesotho	Low middle	92	Sexual health clinic	100% GUD	Clinical diagnosis*	MPCR	54	2	22	14
Htun[15]	1993-94	Lesotho	Low middle	92	Sexual health clinic	100% GUD	Clinical diagnosis*	MPCR	51	4	31	6
Htun[15]	1993-94	Lesotho	Low middle	92	Sexual health clinic	100% GUD	Clinical diagnosis*	MPCR	53	3	32	4

Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Diagnostics	True positive	False negative	False positive	True negative
Ndinya-Achola[29]	1990-91	Kenya	Low middle	156	Primary care	47% males 100% GUD	Clinical diagnosis*	Culture	51	5	76	24
Prabhakar [16]	2008-9	India	Low middle	181	Sexual health clinic	100% male 100% GUD	Clinical diagnosis*	M-PCR	59	31	37	54
Risbud[17]	1994	India	Low middle	302	Sexual health clinic	100% GUD	Clinical diagnosis*	M-PCR	53	31	76	142
Sanchez[7]	1995-6	Dominican Republic	Upper middle	81	General practice	100% male 100% GUD	Clinical diagnosis*	M-PCR	11	10	17	43
Sanchez[7]	1995-6	Peru	Upper middle	63	General practice	100% male 100% GUD	Clinical diagnosis*	M-PCR	0	3	21	39
Fast[20]	1980	Kenya	Low middle	70	"Special treatment clinic"	100% male 100% GUD	Clinical diagnosis*	Culture	42	6	8	14
Dangor[21]	Unclear	South Africa	Upper middle	210	Hospital	100% GUD	Clinical diagnosis*		117	30	14	49

For detection of chancroid using GUD, two studies provided two estimates for pooling. We were unable to conduct a meta-analysis due to too few studies.

Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Diagnostics	True positive	False negative	False positive	True negative
Liu[6]	2003	China	Upper middle	55	Sexual health clinic	100% male 14% GUD	Presence of ulcer	PCR	0	0	53	2
Muralidhar [24]	2013	India	Low middle	90	Sexual health clinic	67% male 7.5% GUD	Clinical diagnosis*	Gram stain, culture, PCR	0	1	10	79

*Clinical diagnosis is based on physical examination and history

3.3 Risk of bias assessment using QUADAS-2

Study	Patient selection	Index Test	Reference standard		Flow and Timing
Behets[8]	Low	Low	Low		Low
Behets[9]	Low	Low	Low		Low
Beyrer[10]	Low	Low	Low		Low
Bhavsar[11]	Low	Low	Low	High[1]	Low
Bogaerts[12]	Low	Low	Low	High[2]	Low
DiCarlo[13]	Low	Low	Low	High[3]	Low
Hina[14]	Low	Low	High		Low
Htun[15]	Low	Low	Low		Low
Prabhakar[16]	Low	Low	Low		Low
Risbud[17]	Low	Low	Low		Low
Sanchez[7]	Low	Low	Low		Low
Wang[18]	Low	Low	Unclear		Low
Wang[19]	Low	Low	Low		Low
Fast[20]	Low	Low	Low	High[4]	Low
Dangor[21]	Low	Low	Low	High[4]	Low
Hanson[28]	Low	Low	Low	High[5]	Low
Ndinya-Achola[29]	Low	Low	High		Low
Das[5]	Low	Low	Unclear		Low
Liu[6]	Low	Low	Unclear		Low
Choudhry[22]	Low	Low	Low	High[5]	Low
Clark[23]	Low	Low	Low		Low
Muralidhar[24]	Low	Low	Low		Low
O'Farrell[25]	Low	Low	Low		Low
Otieno[26]	Low	Low	Low	High[6]	Low
Shah[27]	Low	Low	Low	High[6]	Low
Daly[30]	Low	Low	Low	High[7]	Low
Desai[31]	Low	Low	Low		Low
Shahesmaeili[32]	Low	Low	Low		Low
Tsai[33]	Low	Low	Low		Low
Yu[34]	Low	Low	Low		Low

1 High risk for NG, HD, CG, HSV, Low risk for TP
2 High risk for NG, HD, HSV, Low risk for TP
3 High risk for HD, HSV, Low risk for TP
4 High risk for CT, HD, HSV, Low risk for TP
5 High risk for CT, NG, HD, CG, HSV, Low risk for TP
6 High risk for HSV, Low risk for CT, NG, TP
7 High risk for NG, Low risk for TP
Recommendations from WHO as depicted by Vickerman contrasting 1994 and 2003 algorithms.[59]

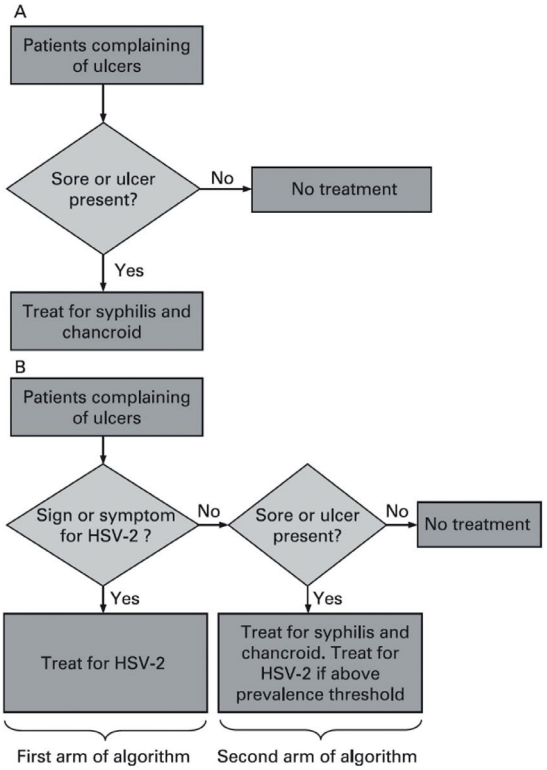


Figure 1 Schematic representation of the 1994 (A) and 2003 (B) WHO algorithms for treating individuals presenting with genital ulcer disease (adapted from WHO[2 18]). Signs for herpes simplex virus (HSV) 2 ulcer include the presence of erosion, open wound or "typical" crops of blisters/vesicles, which can be closed or eroded or crusted depending on duration. The typical herpes ulcer will be small (but can be large if the person is HIV positive), shallow and painful with sensitive inguinal adenopathy. Symptoms for HSV-2 are accompanying pain and burning (typically when contact with urine), tingling sensations (sometimes before the ulcer) and a history of recurrences.

Quite rare to have an explicit evaluation of WHO algorithms[12]

Fig. 1. **WHO flowcharts for the management of genital ulcers** (see ref. (*4*)).

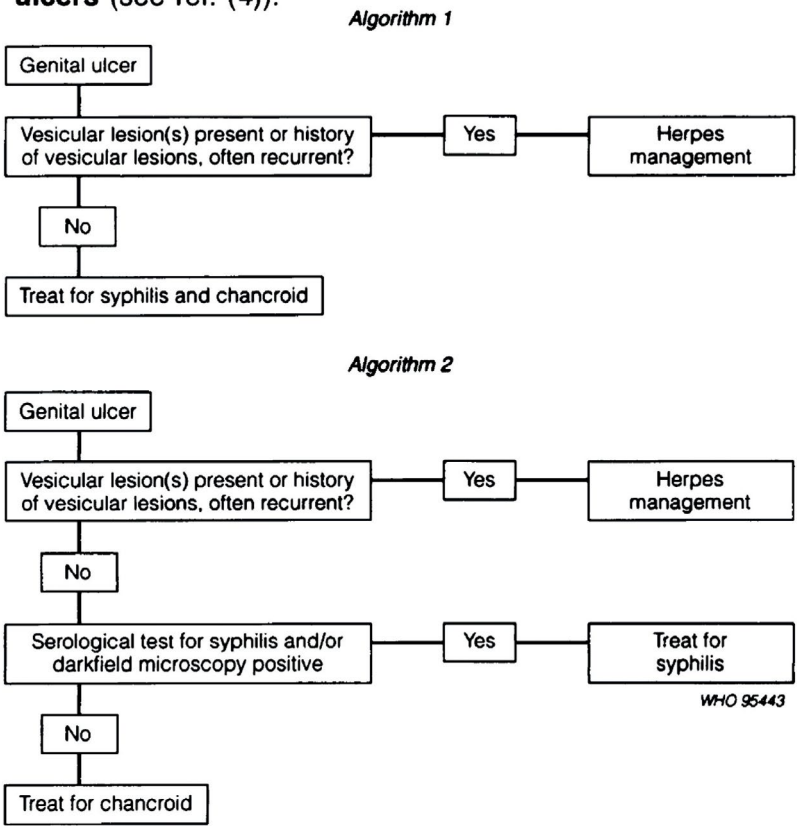
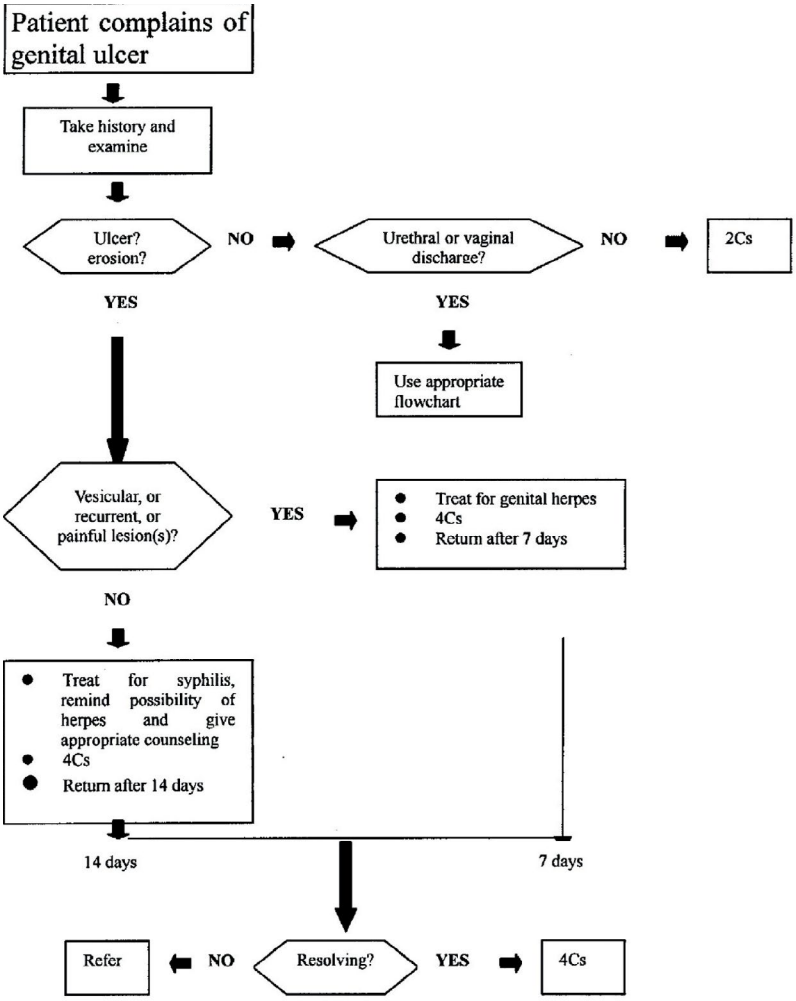


Table 2: **Sensitivity of three diagnostic models (two WHO algorithms and a clinical approach) for the diagnosis of genital herpes, syphilis and chancroid, Kigali, Rwanda**

	Diagnostic model:		
Etiology	Algorithm 1	Algorithm 2	Clinical
Herpes (n = 89)			
No. of diagnoses (total)[a]	8	8	130
No. confirmed by culture	4	4	43
Sensitivity	4.5%	4.5%	48.3%
Syphilis (n = 110)			
No. of diagnoses (total)[a]	387	116	51
No. RPR +ve and TPHA +ve[b]	108	107	20
Sensitivity	98.2%	97.3%	18.2%
Chancroid (n = 115)			
No. of diagnoses (total)[a]	387	271	141
No. confirmed by culture	115	83	74
Sensitivity	100%	72.2%	64.3%

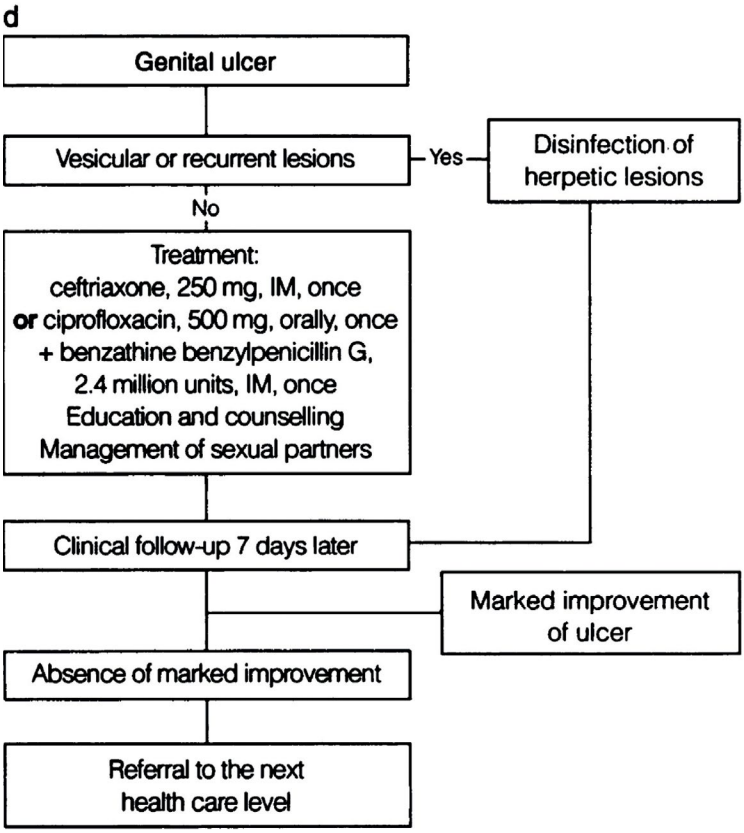
[a] No. of patients treated for the corresponding etiology according to the model.
[b] No. of patients with a reactive rapid plasma reagin (RPR) test and *Treponema pallidum* haemagglutination assay (TPHA).

Chinese algorithm[19]



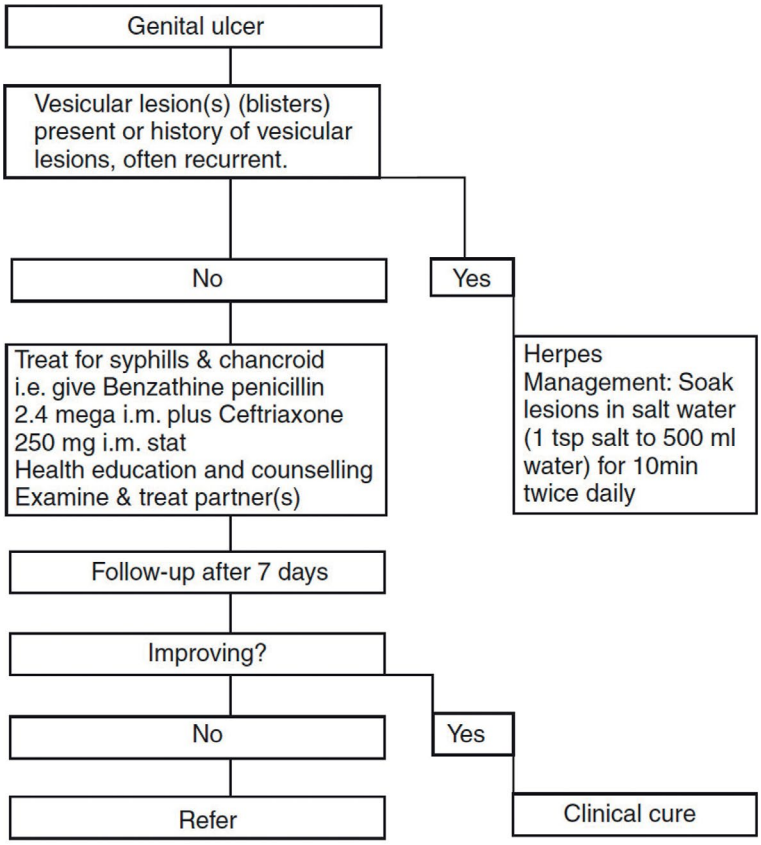
flowchart for the management of genital ulcers in China

Cote d'Ivoire[61]



GUD algorithm used in Botswana[56]

Algorithm 3
Genital ulcer (males and females)



Chinese algorithm[18]

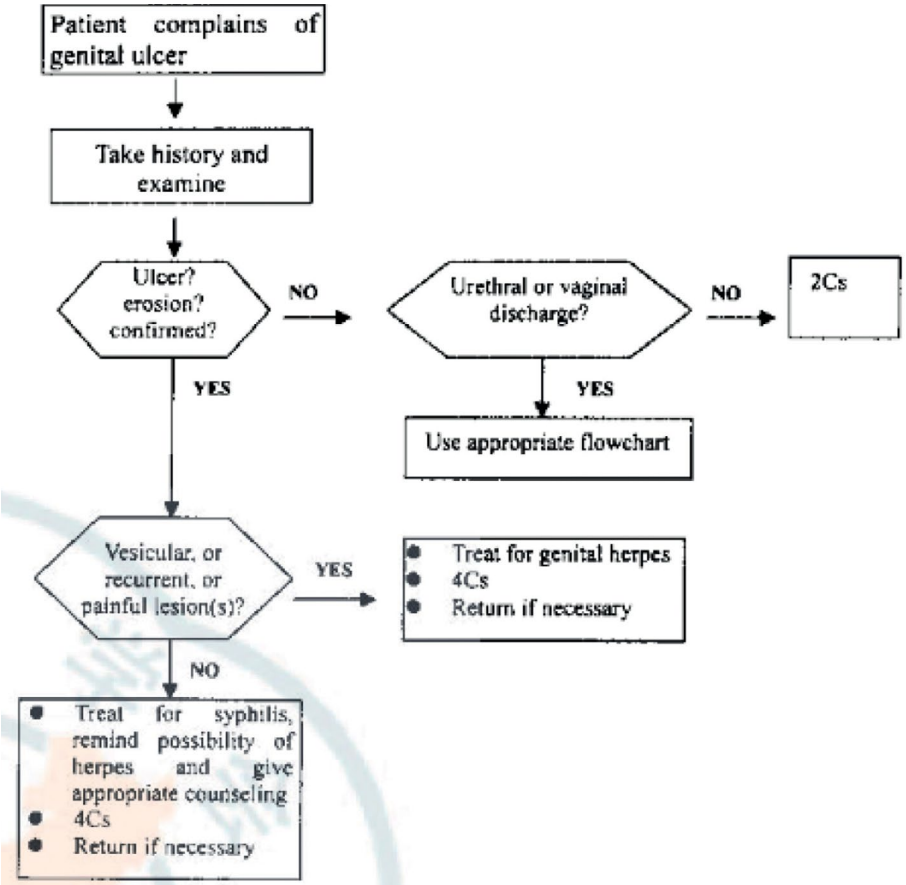


Fig. 3. National flowchart for the management of genital ulcer.

Brazil algorithm[85]

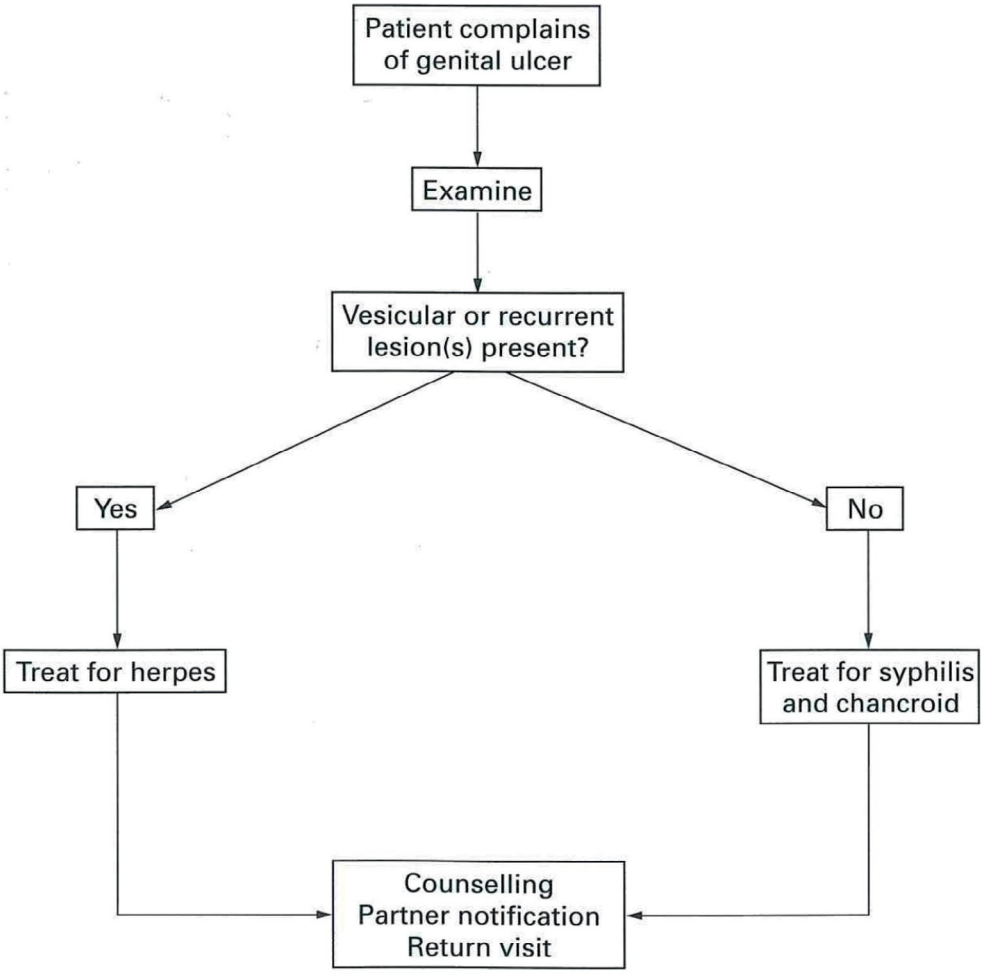


Figure 3 National flow chart for the management of genital ulcer in Brazil.

India's algorithm[16]

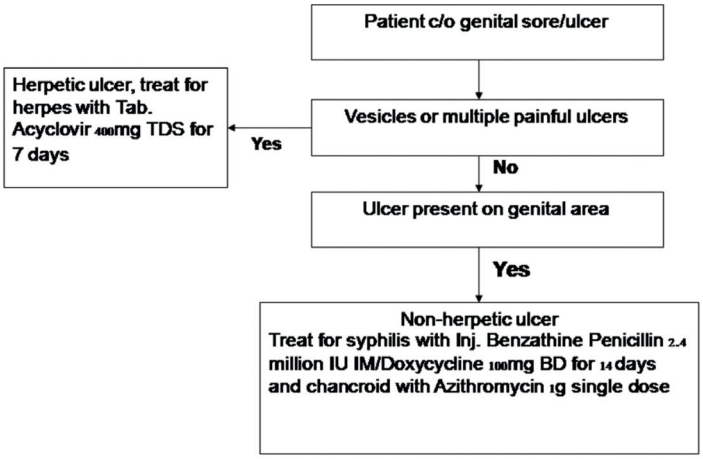


Figure 1. Indian National Syndromic Treatment Flowchart for Genital Ulcer Disease (2007), **Citation:** NACO, Ministry of Health and Family Welfare (2007) (See Ref 8).

Rwanda (1998 publication)[86]

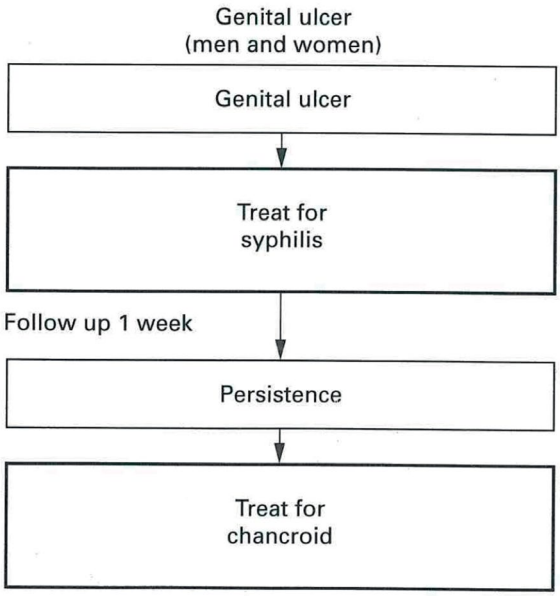


Figure 2 Algorithm for genital ulcer in both men and women.

Aetiology of GUD

155 patients attending outpatient department in hospital, Swaziland (1979)[87]

- 65 HD
- 25 TP
- 18 LGV
- 17 HSV
- 5 Mixed
- 0 none

19 primary health centre, Ethiopia, (2001)[68]

- 2 TP

100 patients from STI clinic in Kenya (1980)[20]

- 6 mixed
- 48 HD
- 6 HSV
- 10 TP
- 0 LGV
- 36 no infections

307 people from STI clinic in Taiwan, China (2002-2004)[34]

- 21 TP

210 people from STI clinic in Rwanda (1986)[98]

- 37 TP
- 32 HSV
- 24 HD
- 13 LGV
- 29 Mixed
- 75 none

227 people from STI clinic in China (2000-2001) [19]

- 78 TP
- 43 HSV
- 28 TP + HSV
- 76 no diagnosis
- 0 HD

96 people from STI clinic in China (1998-1999) [18]

- 23 TP
- 33 HSV
- 40 – no pathogen
- 0 HD

76 people presenting at medical centre in Mozambique (2005)[99]

- 47 HSV
- 3 LGV
- 3 HD
- 0 CG (donovanosis)
- 0 TP
- 23 no diagnosis
- 2 mixed infection (HSV and LGV)

42 women from the health centre and hospital dispensary in Rwanda (1994)[86]

- 34 TP

38 men from the health centre and hospital dispensary in Rwanda (1994)[86]

- 37 TP

81 men from STI clinics in the Dominican Republic(1995-6)[7]

- 5% TP
- 26% HD
- 43% HSV

63 men from STI clinics in Peru (1995-6)[7]

- 10% TP
- 5% HD
- 43% HSV

194 patients from STI clinics in India (2008-9) [16]

- 76 HSV
- 27 TP
- 17 Mixed
- 1 HD

202 patients from general outpatients clinic in Uganda (1999-2001)[38]

- 80 HSV-2
- 7 TP
- 5 HD
- 15 multiple

100 patients from rural Uganda (xx)[36]

- 61 HSV-2
- 5 TP
- 3 HSV-1
- 1 HD
- 1 multiple

398 patients from STI clinic in Malawi (2004-2006)[100]

- 67% HSV2 (serology)
- 15% TP
- 15% HD
- 6% LGV
- 6% mixed
- 20% no aetiology

59 patients attending primary care in the Central African Republic (1993)[58]

- 16 HD
- 20 TP
- 19 HSV
- 10 (2 organisms or more)

298 from STI clinic in the USA (1992-1994)[101]

- 102 HSV
- 75 TP
- 65 HD
- 62 negative
- 7 mixed

240 patients in South Africa in hospital in South Africa (?published 1990)[21]

- 29 no diagnosis
- 37 – mixed
- 147 HD
- 7 HSV
- 52 TP
- 8 LGV
- 1 CG

90 patients attending STI clinic in India (2010-11)[24]

- 6 TP
- 66 HSV
- 0 HD
- 0 LGV
- 0 Donovanosis

105 patients attending STI clinic Lesotho (1993-4)[102]

- 56% HD
- 23% syphilis
- 26% HSV

587 people attending STI clinic in South Africa (2000-2001)[83]

- 48% HSV
- 14% TP
- 11% CT-LGV
- 10% HD
- 1% CG

156 people attending STI clinic in Brazil (1995) [85]

- 31% TP

70 people attending "clinics" in Zimbabwe (2015)[79]

- 17 HSV
- 8 TP
- 1 CT-LGV
- 0 HD

778 people attending STI clinic in Malawi (1992-3)[78]

- 129/758 TP
- 204/778 HD

100 people attending STI clinic in Lesotho (1993-4)[15]

- 56 HD
- 26 HSV
- 23 TP
- 7 CT

137 people attending STD clinic in Malawi (1998-1999)[52]

- 47 HSV
- 41 HD
- 5 TP

136 people attending STD clinic in Malawi (unclear, published 2003)[103]

- 3% TP
- 30% HD
- 35% HSV

304 people from Jamaica[9]

- 158 HSV
- 72 HD
- 31 TP

446 men from a sexual health clinic in the USA (1990-1992)[13]

- 45 TP
- 118 HD
- 57 HSV

98 patients from urban STD clinic in Uganda (date unclear, before 1995)[104]

- 48 HSV
- 11/89 TP

61 attendees of public STD clinic with GUD in Madagascar (1992-93)[105]

- 56% syphilis
- 29% LGV
- 20% chancroid
- 2% HSV

196 attendees of STD clinic with GUD Madagascar (1997)[8]

- 61 HD (chancroid)
- 51 TP
- 15 HSV
- 3 TP and HSV
- 2 HD and TP
- 1 HD and HSV

778 people of STD clinic in Malawi (1992-93)[71]

- 204 HD
- 137 TP

100 people from STI clinic in South Africa (1988-9)[106]

- 40 TP
- 18 HSV
- 16 CG
- 14
- HD
- 6 LGV
- 18 none
- 13 multiple

201 people from STI clinic in India (2008-9)[107]

- 49 HSV
- 20 TP
- 3 CG
- 30 HD
- 1 LGV

100 men from STI clinic in South Africa (1989) [108]

- 29 TP
- 12 HD
- 9 CG
- 9 HSV
- 3 LGV
- 14 Mixed
- 24 none

104 patients, STI clinic, Gambia (before 1987) [88]

- 54 HD
- 23 TP
- 7 LGV
- 6 HSV
- 28 no
- 15 mixed

516 people from STI clinics in the USA (1994) [109]

- 16 HD
- 51 TP
- 320 HSV
- 13 Mixed
- 116 none

53 women from STI clinic in Brazil (2005)[110]

- 28 HSV
- 1 TP

302 patients from STI clinic in India (1994)[17]

- 79 HSV
- 69 HD
- 29 TP
- 7% multiple
- 104 none

100 people from community cohort in Uganda (2002-6)[36]

- 64 HSV
- 1 HD
- 29 none
- 5 TP
- 1 mixed

613 men from primary health care in South Africa (2005-6)[111]

- 451 HSV
- 30 TP
- 10 HD
- 126 none

813 individuals from India (2004-6)[112]

- 8 TP
- 79 HSV-2
- 0 HD

143 people from STI clinic in the USA (1994-5) [113]

- 47 HD
- 16 TP
- 39 HSV
- 12 Mixed
- 29 none

372 people from STI clinic in Amsterdam (1996) [114]

- 208 HSV
- 12 TP
- 3 HD

4. REFERENCES

1. World Health Organization. (2021). Guidelines for the management of symptomatic sexually transmitted infections. World Health Organization. https://apps.who.int/iris/handle/10665/342523. License: CC BY-NC-SA 3.0 IGO.
2. Cochrane Handbook for Systematic Reviews of Interventions version 5.1 [Available from: https://training.cochrane.org/handbook.
3. Joanna Briggs Institute Reviewer's Manual. Diagnostic test accuracy systematic reviews. Appendix 9.1 Critical appraisal checklist [Available from: https://wiki.joannabriggs.org/display/MANUAL/Appendix+9.1+Critical+appraisal+checklist.
4. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med. 2001;20(19):2865-84.
5. Das A, Ghosh P, Ghosh I, Bhattacharya R, Azad Sardar AK, Goswami S, et al. Usefulness and Utility of NACO Regime in the Management of Sexually Transmitted Infections: A Pilot Study. Indian Journal of Dermatology. 2017;62(6):630-4.
6. Liu H, Jamison D, Li X, Ma E, Yin Y, Detels R. Is syndromic management better than the current approach for treatment of STDs in China? Evaluation of the cost-effectiveness of syndromic management for male STD patients. Sexually Transmitted Diseases. 2003;30(4):327-30.
7. Sanchez J, Volquez C, Totten PA, Campos PE, Ryan C, Catlin M, et al. The etiology and management of genital ulcers in the Dominican Republic and Peru. Sexually Transmitted Diseases. 2002;29(10):559-67.
8. Behets FM, Andriamiadana J, Randrianasolo D, Randriamanga R, Rasamilalao D, Chen CY, et al. Chancroid, primary syphilis, genital herpes, and lymphogranuloma venereum in Antananarivo, Madagascar. Journal of Infectious Diseases. 1999;180(4):1382-5.
9. Behets FM, Brathwaite AR, Hylton-Kong T, Chen CY, Hoffman I, Weiss JB, et al. Genital ulcers: etiology, clinical diagnosis, and associated human immunodeficiency virus infection in Kingston, Jamaica. Clinical Infectious Diseases. 1999;28(5):1086-90.
10. Beyrer C, Jitwatcharanan K, Natpratan C, Kaewvichit R, Nelson KE, Chen CY, et al. Molecular methods for the diagnosis of genital ulcer disease in a sexually transmitted disease clinic population in northern Thailand: predominance of herpes simplex virus infection. Journal of Infectious Diseases. 1998;178(1):243-6.
11. Bhavsar C, Patel RM, Marfatia Y. A study of 113 cases of genital ulcerative disease and urethral discharge syndrome with validation of syndromic management of sexually transmitted diseases. Indian Journal Of Sexually Transmitted Diseases And AIDS. 2014;35(1):35-9.
12. Bogaerts J, Vuylsteke B, Martinez Tello W, Mukantabana V, Akingeneye J, Laga M, et al. Simple algorithms for the management of genital ulcers: evaluation in a primary health care centre in Kigali, Rwanda. Bulletin of the World Health Organization. 1995;73(6):761-7.
13. DiCarlo RP, Martin DH. The clinical diagnosis of genital ulcer disease in men. Clin Infect Dis. 1997;25(2):292-8.

14. Hina R, Tankhiwale SS, Surpam RB. Study of seroprevalence and syndromic validation of HSV2 among genito-ulcerative disease patients attending STI clinic in a tertiary care hospital. Journal of Evolution of Medical and Dental Sciences. 2017;6(36):2984-6.

15. Htun Y, Morse SA, Dangor Y, Fehler G, Radebe F, Trees DL, et al. Comparison of clinically directed, disease specific, and syndromic protocols for the management of genital ulcer disease in Lesotho. Sexually Transmitted Infections. 1998;74 Suppl 1:S23-8.

16. Prabhakar P, Narayanan P, Deshpande GR, Das A, Neilsen G, Mehendale S, et al. Genital ulcer disease in India: etiologies and performance of current syndrome guidelines. Sexually Transmitted Diseases. 2012;39(11):906-10.

17. Risbud A, Chan-Tack K, Gadkari D, Gangakhedkar RR, Shepherd ME, Bollinger R, et al. The etiology of genital ulcer disease by multiplex polymerase chain reaction and relationship to HIV infection among patients attending sexually transmitted disease clinics in Pune, India. Sex Transm Dis. 1999;26(1):55-62.

18. Wang Q, Yang P, Zhong M, Wang G. Validation of diagnostic algorithms for syndromic management of sexually transmitted diseases. Chinese Medical Journal. 2003;116(2):181-6.

19. Wang QQ, Mabey D, Peeling RW, Tan ML, Jian DM, Yang P, et al. Validation of syndromic algorithm for the management of genital ulcer diseases in China. International Journal of STD & AIDS. 2002;13(7):469-74.

20. Fast MV, D'Costa LJ, Nsanze H, Piot P, Curran J, Karasira P, et al. The clinical diagnosis of genital ulcer disease in men in the tropics. Sex Transm Dis. 1984;11(2):72-6.

21. Dangor Y, Ballard RC, da LEF, Fehler G, Miller SD, Koornhof HJ. Accuracy of clinical diagnosis of genital ulcer disease. Sex Transm Dis. 1990;17(4):184-9.

22. Choudhry S, Ramachandran VG, Das S, Bhattacharya SN, Mogha NS. Pattern of sexually transmitted infections and performance of syndromic management against etiological diagnosis in patients attending the sexually transmitted infection clinic of a tertiary care hospital. Indian Journal Of Sexually Transmitted Diseases And AIDS. 2010;31(2):104-8.

23. Clark JL, Lescano AG, Konda KA, Leon SR, Jones FR, Klausner JD, et al. Syndromic management and STI control in urban Peru. PLoS ONE. 2009;4(9):e7201.

24. Muralidhar S, Talwar R, Anil Kumar D, Kumar J, Bala M, Khan N, et al. Genital Ulcer Disease: How Worrisome Is It Today? A Status Report from New Delhi, India. Journal of Sexually Transmitted Diseases Print. 2013;2013:203636.

25. O'Farrell N, Morison L, Moodley P, Pillay K, Vanmali T, Quigley M, et al. High-risk sexual behaviour in men attending a sexually transmitted infection clinic in Durban, South Africa. Sexually Transmitted Infections. 2007;83(7):530-3.

26. Otieno FO, Ndivo R, Oswago S, Ondiek J, Pals S, McLellan-Lemal E, et al. Evaluation of syndromic management of sexually transmitted infections within the Kisumu Incidence Cohort Study. International Journal of STD & AIDS. 2014;25(12):851-9.

27. Shah NS, Kim E, de Maria Hernandez Ayala F, Guardado Escobar ME, Nieto AI, Kim AA, et al. Performance and comparison of self-reported STI symptoms among high-risk populations - MSM, sex workers, persons living with HIV/AIDS - in El Salvador. International Journal of STD & AIDS. 2014;25(14):984-91.

28. Hanson S, Sunkutu RM, Kamanga J, Hojer B, Sandstrom E. STD care in Zambia: an evaluation of the guidelines for case management through a syndromic approach. International Journal of STD & AIDS. 1996;7(5):324-32.

29. Ndinya-Achola JO, Kihara AN, Fisher LD, Krone MR, Plummer FA, Ronald A, et al. Presumptive specific clinical diagnosis of genital ulcer disease (GUD) in a primary health care setting in Nairobi. International Journal of STD & AIDS. 1996;7(3):201-5.

30. Daly CC, Maggwa N, Mati JK, Solomon M, Mbugua S, Tukei PM, et al. Risk factors for gonorrhoea, syphilis, and trichomonas infections among women attending family planning clinics in Nairobi, Kenya. Genitourinary Medicine. 1994;70(3):155-61.

31. Desai VK, Kosambiya JK, Thakor HG, Umrigar DD, Khandwala BR, Bhuyan KK. Prevalence of sexually transmitted infections and performance of STI syndromes against aetiological diagnosis, in female sex workers of red light area in Surat, India. Sexually Transmitted Infections. 2003;79(2):111-5.

32. Shahesmaeili A, Karamouzian M, Shokoohi M, Kamali K, Fahimfar N, Nadji SA, et al. Symptom-Based Versus Laboratory-Based Diagnosis of Five Sexually Transmitted Infections in Female Sex Workers in Iran. Aids and Behavior. 2018;22:S19-S25.

33. Tsai CH, Lee TC, Chang HL, Tang LH, Chiang CC, Chen KT. The cost-effectiveness of syndromic management for male sexually transmitted disease patients with urethral discharge symptoms and genital ulcer disease in Taiwan. Sexually Transmitted Infections. 2008;84(5):400-4.

34. Yu MC, Li LH, Lu TH, Tang LH, Tsai CH, Chen KT. Aetiology of sexually transmitted disease (STD) and comparison of STD syndromes and aetiological diagnosis in Taipei, Taiwan. Clinical Microbiology & Infection. 2005;11(11):914-8.

35. Paz-Bailey G, Rahman M, Chen C, Ballard R, Moffat HJ, Kenyon T, et al. Changes in the etiology of sexually transmitted diseases in Botswana between 1993 and 2002: implications for the clinical management of genital ulcer disease. Clin Infect Dis. 2005;41(9):1304-12.

36. Suntoke TR, Hardick A, Tobian AA, Mpoza B, Laeyendecker O, Serwadda D, et al. Evaluation of multiplex real-time PCR for detection of Haemophilus ducreyi, Treponema pallidum, herpes simplex virus type 1 and 2 in the diagnosis of genital ulcer disease in the Rakai District, Uganda. Sex Transm Infect. 2009;85(2):97-101.

37. Lai W, Chen CY, Morse SA, Htun Y, Fehler HG, Liu H, et al. Increasing relative prevalence of HSV-2 infection among men with genital ulcers from a mining community in South Africa. Sex Transm Infect. 2003;79(3):202-7.

38. Pickering JM, Whitworth JA, Hughes P, Kasse M, Morgan D, Mayanja B, et al. Aetiology of sexually transmitted infections and response to syndromic treatment in southwest Uganda. Sexually Transmitted Infections. 2005;81(6):488-93.

39. Paz-Bailey G, Rahman M, Chen C, Ballard R, Moffat HJ, Kenyon T, et al. Changes in the etiology of sexually transmitted diseases in Botswana between 1993 and 2002: implications for the clinical management of genital ulcer disease. Clinical Infectious Diseases. 2005;41(9):1304-12.

40. Mayaud P, Mabey D. Approaches to the control of sexually transmitted infections in developing countries: old problems and modern challenges. Sex Transm Infect. 2004;80(3):174-82.

41. O'Farrell N, Hoosen AA, Coetzee KD, van den Ende J. Sexual behaviour in Zulu men and women with genital ulcer disease. Genitourin Med. 1992;68(4):245-8.

42. Dickerson MC, Johnston J, Delea TE, White A, Andrews E. The causal role for genital ulcer disease as a risk factor for transmission of human immunodeficiency virus. An application of the Bradford Hill criteria. Sex Transm Dis. 1996;23(5):429-40.

43. Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Senkoro K, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. Lancet. 1995;346(8974):530-6.

44. Kamali A, Quigley M, Nakiyingi J, Kinsman J, Kengeya-Kayondo J, Gopal R, et al. Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. Lancet. 2003;361(9358):645-52.

45. Nilsen AE, Aasen T, Halsos AM, Kinge BR, Tjotta EA, Wikstrom K, et al. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. Lancet. 1982;2(8298):571-3.

46. Bryson YJ, Dillon M, Lovett M, Acuna G, Taylor S, Cherry JD, et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir. A randomized double-blind controlled trial in normal subjects. N Engl J Med. 1983;308(16):916-21.

47. Reichman RC, Badger GJ, Mertz GJ, Corey L, Richman DD, Connor JD, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir. A controlled trial. JAMA. 1984;251(16):2103-7.

48. Garcia PJ, Holmes KK, Carcamo CP, Garnett GP, Hughes JP, Campos PE, et al. Prevention of sexually transmitted infections in urban communities (Peru PREVEN): a multicomponent community-randomised controlled trial. Lancet. 2012;379(9821):1120-8.

49. Van Dyck E, Piot P. Laboratory techniques in the investigation of chancroid, lymphogranuloma venereum and donovanosis. Genitourin Med. 1992;68(2):130-3.

50. Koutsky LA, Stevens CE, Holmes KK, Ashley RL, Kiviat NB, Critchlow CW, et al. Underdiagnosis of genital herpes by current clinical and viral-isolation procedures. N Engl J Med. 1992;326(23):1533-9.

51. World Health Organization. Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people. 2011. [Available from: http://apps.who.int/iris/bitstream/10665/44619/1/9789241501750_eng.pdf.

52. Hoyo C, Hoffman I, Moser BK, Hobbs MM, Kazembe P, Krysiak RG, et al. Improving the accuracy of syndromic diagnosis of genital ulcer disease in Malawi. Sexually Transmitted Diseases. 2005;32(4):231-7.

53. McCormick DF, Rahman M, Zadrozny S, Alam A, Ashraf L, Neilsen GA, et al. Prevention and control of sexually transmissible infections among hotel-based female sex workers in Dhaka, Bangladesh. Sexual Health. 2013;10(6):478-86.

54. Meda N, Sangare L, Lankoande S, Sanou PT, Compaore PI, Catraye J, et al. Pattern of sexually transmitted diseases among pregnant women in Burkina Faso, west Africa: potential for a clinical management based on simple approaches. Genitourinary Medicine. 1997;73(3):188-93.

55. Adams EJ, Garcia PJ, Garnett GP, Edmunds WJ, Holmes KK. The cost-effectiveness of syndromic management in pharmacies in Lima, Peru. Sexually Transmitted Diseases. 2003;30(5):379-87.

56. Boonstra E, Lindbaek M, Klouman E, Ngome E, Romoren M, Sundby J. Syndromic management of sexually transmitted diseases in Botswana's primary health care: quality of care aspects. Tropical Medicine & International Health. 2003;8(7):604-14.

57. Gilson L, Mkanje R, Grosskurth H, Mosha F, Picard J, Gavyole A, et al. Cost-effectiveness of improved treatment services for sexually transmitted diseases in preventing HIV-1 infection in Mwanza Region, Tanzania. Lancet. 1997;350(9094):1805-9.

58. Parker KA, Koumans EH, Hawkins RV, Massanga M, Somse P, Barker K, et al. Providing low-cost sexually transmitted diseases services in two semi-urban health centers in Central African Republic (CAR): characteristics of patients and patterns of health care-seeking behavior. Sexually Transmitted Diseases. 1999;26(9):508-16.

59. Vickerman P, Ndowa F, Mayaud P. Modelling the cost per ulcer treated of incorporating episodic treatment for HSV-2 into the syndromic algorithm for genital ulcer disease. Sexually Transmitted Infections. 2008;84(3):243-8.

60. White RG, Moodley P, McGrath N, Hosegood V, Zaba B, Herbst K, et al. Low effectiveness of syndromic treatment services for curable sexually transmitted infections in rural South Africa. Sexually Transmitted Infections. 2008;84(7):528-34.

61. La Ruche G, Lorougnon F, Digbeu N. Therapeutic algorithms for the management of sexually transmitted diseases at the peripheral level in Cote d'Ivoire: assessment of efficacy and cost. Bull World Health Organ. 1995;73(3):305-13.

62. Banwat EB, Egah DZ, Peter J, Barau C, Majang Y, Mafuyai S, et al. Integrating syndromic case management of sexually transmitted diseases into primary healthcare services in Nigeria. Nigerian Journal of Medicine: Journal of the National Association of Resident Doctors of Nigeria. 2009;18(2):215-8.

63. Khandwalla HE, Luby S, Rahman S. Knowledge, attitudes, and practices regarding sexually transmitted infections among general practitioners and medical specialists in Karachi, Pakistan. Sex Transm Infect. 2000;76(5):383-5.

64. Uchenna C, Govender I. Knowledge, attitudes and practices of doctors at Jubilee Hospital, Tshwane District, regarding the syndromic management guidelines for sexually transmitted infections. South African Family Practice. 2018;60(5):155-61.

65. Nuwaha F. Determinants of choosing public or private health care among patients with sexually transmitted infections in Uganda. Sex Transm Dis. 2006;33(7):422-7.

66. Grosskurth H, Mwijarubi E, Todd J, Rwakatare M, Orroth K, Mayaud P, et al. Operational performance of an STD control programme in Mwanza Region, Tanzania. Sexually Transmitted Infections. 2000;76(6):426-36.

67. Beyene M, Gizachew Y, Afework K, Berihun M, Shitaye A, Bemnet A, et al. Sexually transmitted infections based on the syndromic approach in Gondar town, northwest Ethiopia: a retrospective cross-sectional study. BMC Public Health. 2013;13(143).

68. Wolday D, Z GM, Mohammed Z, Meles H, Messele T, Seme W, et al. Risk factors associated with failure of syndromic treatment of sexually transmitted diseases among women seeking primary care in Addis Ababa. Sex Transm Infect. 2004;80(5):392-4.

69. Cheluget B, Joesoef MR, Marum LH, Wandera C, Ryan CA, Decock KM, et al. Changing patterns in sexually transmitted disease syndromes in Kenya after the introduction of a syndromic management program. Sexually Transmitted Diseases. 2004;31(9):522-5.

70. Chilongozi DA, Daly CC, Franco L, Liomba NG, Dallabetta G. Sexually transmitted diseases: a survey of case management in Malawi. International Journal of STD & AIDS. 1996;7(4):269-75.

71. Behets FM, Liomba G, Lule G, Dallabetta G, Hoffman IF, Hamilton HA, et al. Sexually transmitted diseases and human immunodeficiency virus control in Malawi: a field study of genital ulcer disease. J Infect Dis. 1995;171(2):451-5.

72. Garcia PJ, Gotuzzo E, Hughes JP, Holmes KK. Syndromic management of STDs in pharmacies: evaluation and randomised intervention trial. Sexually Transmitted Infections. 1998;74(Suppl 1):S153-8.

73. Goel SS. Study of syndromic management approach in the management of sexually transmitted diseases in rural population. Indian Journal of Sexually Transmitted Diseases. 2012;33(2):146-7.

74. Mertens TE, Smith GD, Kantharaj K, Mugrditchian D, Radhakrishnan KM. Observations of sexually transmitted disease consultations in India. Public Health. 1998;112(2):123-8.

75. Sharma K, Chavan Y, Aras R, Khismatrao D. Syndromic management of STDs in a male health clinic in a primary health care setting. Indian Journal of Sexually Transmitted Diseases. 2011;32(2):136-7.

76. Tankhiwale SS, Chavan SP. Comparative study of syndromic and etiological diagnosis of sexually transmitted infection except human immunodeficiency virus in sexually transmitted infection and reproductive tract infection clinic attendees in central India. International Journal of Medicine and Public Health. 2013;3(4):347-51.

77. Iipinge SN, Pretorius L. The delivery and quality of sexually transmitted infections treatment by private general practitioners in Windhoek Namibia. Global Journal of Health Science. 2012;4(5):156-71.

78. Lule G, Behets FMT, Hoffman IF, Liomba G, Dallabetta G, Hamilton HA, et al. Choosing an effective and affordable antibiotic regimen for sexually transmitted diseases (STD) patients in Malawi. Malawi Medical Journal. 1998;11:50-5.

79. Machiha A, Mugurungi O, Tshimanga M, Kilmarx P, Mungati M, Nyakura J, et al. P09.24 The aetiology of genital ulcer disease and association with HIV infection in Zimbabwe. Sexually Transmitted Infections. 2015;91:A157.

80. Mahmood MA, Saniotis A. Use of syndromic management algorithm for sexually transmitted infections and reproductive tract infections management in community settings in Karachi. Journal of the Pakistan Medical Association. 2011;61(5):453-7.

81. Mark J, Hariri S, Ilunga R, Forhan S, Likibi M, M LK, et al. Evaluation of sexually transmitted infection clinical services in gauteng province, South Africa: Knowledge, attitudes, and beliefs among health care providers. Sexually Transmitted Infections. 2011;87:A92-A3.

82. Mathews C, van Rensburg A, Coetzee N. The sensitivity of a syndromic management approach in detecting sexually transmitted diseases in patients at a public health clinic in Cape Town. South African Medical Journal Suid-Afrikaanse Tydskrif Vir Geneeskunde. 1998;88(10):1337-40.

83. Moodley P, Sturm PD, Vanmali T, Wilkinson D, Connolly C, Sturm AW. Association between HIV-1 infection, the etiology of genital ulcer disease, and response to syndromic management. Sexually Transmitted Diseases. 2003;30(3):241-5.

84. Schneider H, Blaauw D, Dartnall E, Coetzee DJ, Ballard RC. STD care in the South African private health sector. South African Medical Journal Suid-Afrikaanse Tydskrif Vir Geneeskunde. 2001;91(2):151-6.

85. Moherdaui F, Vuylsteke B, Siqueira LF, dos Santos Junior MQ, Jardim ML, de Brito AM, et al. Validation of national algorithms for the diagnosis of sexually transmitted diseases in Brazil: results from a multicentre study. Sexually Transmitted Infections. 1998;74 Suppl 1:S38-43.

86. Steen R, Soliman C, Mujyambwani A, Twagirakristu JB, Bucyana S, Grundmann C, et al. Notes from the field: practical issues in upgrading STD services based on experience from primary healthcare facilities in two Rwandan towns. Sexually Transmitted Infections. 1998;74 Suppl 1:S159-65.

87. Meheus A, Van Dyck E, Ursi JP, Ballard RC, Piot P. Etiology of genital ulcerations in Swaziland. Sex Transm Dis. 1983;10(1):33-5.

88. Mabey DC, Wall RA, Bello CS. Aetiology of genital ulceration in the Gambia. Genitourin Med. 1987;63(5):312-5.

89. Mbofana FS, Brito FJ, Saifodine A, Cliff JL. Syndromic management of sexually transmitted diseases at primary care level, Mozambique. Sex Transm Infect. 2002;78(1):E2.

90. Leiva A, Shaw M, Paine K, Manneh K, McAdam K, Mayaud P. Management of sexually transmitted diseases in urban pharmacies in The Gambia. International Journal of STD & AIDS. 2001;12(7):444-52.

91. Harrison A, Wilkinson D, Lurie M, Connolly AM, Karim SA. Improving quality of sexually transmitted disease case management in rural South Africa. AIDS. 1998;12(17):2329-35.

92. Wilkinson D, Karim SS, Lurie M, Harrison A. Public-private health sector partnerships for STD control in South Africa--perspectives from the Hlabisa experience. S Afr Med J. 2001;91(6):517-20.

93. Iipinge SN, Pretorius L. The delivery and quality of sexually transmitted infections treatment by private general practitioners in Windhoek Namibia. Glob J Health Sci. 2012;4(5):156-71.

94. Bitera R, Alary M, Masse B, Viens P, Lowndes C, Baganizi E, et al. [Quality of disease management of sexually transmitted diseases: investigation of care in six countries in West Africa]. Sante. 2002;12(2):233-9.

95. Alemayehu A, Godana W. Knowledge and Practice of Clinicians regarding Syndromic Management of Sexually Transmitted Infections in Public Health Facilities of Gamo Gofa Zone, South Ethiopia. J Sex Transm Dis. 2015;2015:310409.

96. Ward K, Butler N, Mugabo P, Klausner J, McFarland W, Chen S, et al. Provision of syndromic treatment of sexually transmitted infections by community pharmacists: a potentially underutilized HIV prevention strategy. Sexually Transmitted Diseases. 2003;30(8):609-13.

97. Sharma R, Prajapati S, Patel B, Kumar P. Evaluation of Skill-oriented Training on Enhanced Syndromic Case Management (ESCM) of Reproductive Tract Infections / Sexually Transmitted Infections (RTI/STIs) of Care Providers from Three-tier Health-care System of Gujarat. Indian Journal of Community Medicine. 2016;41(6):183-9.

98. Bogaerts J, Ricart CA, Van Dyck E, Piot P. The etiology of genital ulceration in Rwanda. Sex Transm Dis. 1989;16(3):123-6.

99. Zimba TF, Apalata T, Sturm WA, Moodley P. Aetiology of sexually transmitted infections in Maputo, Mozambique. Journal of Infection in Developing Countries. 2011;5(1):41-7.

100. Phiri S, Zadrozny S, Weiss HA, Martinson F, Nyirenda N, Chen CY, et al. Etiology of genital ulcer disease and association with HIV infection in Malawi. Sexually Transmitted Diseases. 2013;40(12):923-8.

101. Orle KA, Gates CA, Martin DH, Body BA, Weiss JB. Simultaneous PCR detection of Haemophilus ducreyi, Treponema pallidum, and herpes simplex virus types 1 and 2 from genital ulcers. J Clin Microbiol. 1996;34(1):49-54.

102. Morse SA, Trees DL, Htun Y, Radebe F, Orle KA, Dangor Y, et al. Comparison of clinical diagnosis and standard laboratory and molecular methods for the diagnosis of genital ulcer disease in lesotho: Association with human immunodeficiency virus infection. Journal of Infectious Diseases. 1997;175(3):583-9.

103. Hoyo C, Hoffman I, Moser BK, Hobbs M. Syndromic criteria to improve GUD diagnosis. American Journal of Epidemiology. 2003;157(11):S47-S.

104. Kamya MR, Nsubuga P, Grant RM, Hellman N. The high prevalence of genital herpes among patients with genital ulcer disease in Uganda. Sex Transm Dis. 1995;22(6):351-4.

105. Harms G, Matull R, Randrianasolo D, Andriamiadana J, Rasamindrakotroka A, Kirsch T, et al. Pattern of sexually transmitted diseases in a Malagasy population. Sex Transm Dis. 1994;21(6):315-20.

106. O'Farrell N, Hoosen AA, Coetzee KD, van den Ende J. Genital ulcer disease in women in Durban, South Africa. Genitourin Med. 1991;67(4):322-6.

107. Vora R, Anjaneyan G, Doctor C, Gupta R. Clinico-epidemiological study of sexually transmitted infections in males at a rural-based tertiary care center. Indian J Sex Transm Dis AIDS. 2011;32(2):86-9.

108. O'Farrell N, Hoosen AA, Coetzee KD, van den Ende J. Genital ulcer disease in men in Durban, South Africa. Genitourin Med. 1991;67(4):327-30.

109. Mertz KJ, Trees D, Levine WC, Lewis JS, Litchfield B, Pettus KS, et al. Etiology of genital ulcers and prevalence of human immunodeficiency virus coinfection in 10 US cities. The Genital Ulcer Disease Surveillance Group. J Infect Dis. 1998;178(6):1795-8.

110. Gomes CM, Giraldo PC, Gomes Fde A, Amaral R, Passos MR, Goncalves AK. Genital ulcers in women: clinical, microbiologic and histopathologic characteristics. Braz J Infect Dis. 2007;11(2):254-60.

111. Lewis DA, Muller E, Steele L, Sternberg M, Radebe F, Lyall M, et al. Prevalence and associations of genital ulcer and urethral pathogens in men presenting with genital ulcer syndrome to primary health care clinics in South Africa. Sex Transm Dis. 2012;39(11):880-5.

112. Becker M, Stephen J, Moses S, Washington R, Maclean I, Cheang M, et al. Etiology and determinants of sexually transmitted infections in Karnataka state, south India. Sex Transm Dis. 2010;37(3):159-64.

113. Mertz KJ, Weiss JB, Webb RM, Levine WC, Lewis JS, Orle KA, et al. An investigation of genital ulcers in Jackson, Mississippi, with use of a multiplex polymerase chain reaction assay: high prevalence of chancroid and human immunodeficiency virus infection. J Infect Dis. 1998;178(4):1060-6.

114. Bruisten SM, Cairo I, Fennema H, Pijl A, Buimer M, Peerbooms PG, et al. Diagnosing genital ulcer disease in a clinic for sexually transmitted diseases in Amsterdam, The Netherlands. J Clin Microbiol. 2001;39(2):601-5.

5. APPENDIX A – SEARCH RESULTS

5.1 Genital ulcers syndromes

The search retrieved a total of 14,190- results. 4286 (30%) were identified as duplicates. The number of results pre-and post-deduplication is listed in the table below.

Database name	Diagnostic accuracy: Total number of results	Diagnostic accuracy: Number of results once duplicates removed	Other papers: Total number of results	Other papers: Number of results once duplicates removed
Ovid SP Medline and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily	1753	1748	941	940
OvidSP Embase	4687	3564	2590	2063
OvidSP Global Health	1159	428	398	202
OvidSP Northern Light Life Sciences Conference Abstracts	60	30	74	39
Ebsco CINAHL Plus	526	120	470	209
Ebsco Africa-Wide Information	287	26	63	13
Clarivate Analytics Web of Science Core Collection	893	346	216	108
BIREME/PAHO/WHO Virtual Health Library LILACS	44	41	29	27
Total	**9409**	**6303**	**4781**	**3601**

For more information, contact:

World Health Organization
Department of Global HIV,
Hepatitis and STI Programme
20, avenue Appia
1211 Geneva 27
Switzerland

Email: hiv-aids@who.int

www.who.int/hiv

9789240034822