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Sexual Orientation and HIV Coinfection Among Serofast Syphilis Patients: A Retrospective Analysis in Surakarta, Indonesia

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A B S T R A C T

Introduction: Syphilis and its serofast state — persistent low-level non-treponemal reactivity after adequate therapy — complicate the assessment of cure, particularly where HIV coinfection is common, and Indonesian data are scarce. This study profiled serofast syphilis patients and compared the determinants of HIV coinfection.

Methods: Retrospective analytic review of electronic medical records of all serofast syphilis patients attending Dr. Moewardi Regional General Hospital, Surakarta (January 2020–April 2026). Proportions are reported with 95% confidence intervals (CI); HIV-positive and HIV-negative groups were compared by Fisher exact and chi-square tests with odds ratios (OR) and Cramér's V, multivariable logistic regression and receiver-operating-characteristic (ROC) analysis.

Results: Of 46 patients, 91.3% were male, 45.7% aged 20–30 years, 39.1% had late latent syphilis, and 80.4% were HIV-coinfected (95% CI 66.8–89.3). Men who have sex with men accounted for 73.9% and strongly predicted HIV coinfection (OR 17.73, 95% CI 3.26–96.34; p<0.001; adjusted OR 41.56; AUC 0.838). Other characteristics were similar, and estimates were imprecise given the small comparison group.

Conclusion: Serofast syphilis in this setting reflects a young, male, MSM, HIV-coinfected population; sexual orientation best distinguishes coinfection, supporting integrated HIV monitoring rather than reflexive re-treatment.

1. Introduction

Syphilis, caused by the spirochete *Treponema pallidum* subspecies pallidum, remains one of the most prevalent sexually transmitted infections worldwide and has resurged markedly over the past decade.[1,2] The World Health Organization estimated that 8 million adults aged 15–49 years acquired syphilis in 2022, and surveillance from the United States and China has documented increases of up to 80% in reported cases since 2018, accompanied by a steep rise in congenital syphilis.[2,3] In China, incidence rose from 4.50 to 34.04 per 100,000 population over

less than two decades, making syphilis the most frequently reported notifiable sexually transmitted infection in several jurisdictions.[3,4] In Indonesia, the Ministry of Health recorded tens of thousands of new cases annually, and the burden is concentrated within key populations, especially men who have sex with men (MSM) and people living with HIV.[5,6]

The success of syphilis therapy is judged serologically. A fourfold (two-dilution) decline in non-treponemal antibody titres — measured by the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin tests — within 6 to 12 months of adequate treatment is the conventional marker of response.[7,8] A substantial minority of patients, however, fail to achieve this decline despite appropriate therapy and in the absence of clinical reinfection. This phenomenon, termed the serofast state, describes persistent low-level non-treponemal reactivity that neither resolves nor declines significantly after adequate treatment.[9,10] The serofast state occurs in approximately 20–40% of treated patients and represents a genuine clinical dilemma, since it confounds the evaluation of cure and complicates decisions about re-treatment, lumbar puncture and ongoing follow-up.[11-13]

The pathogenesis of the serofast state is incompletely understood. Rather than reflecting treatment failure, it is thought to arise from host immune dysregulation, persistent low-grade antigenic stimulation, an imbalance between pro-inflammatory and anti-inflammatory cytokines, and the considerable antigenic variation of *T. pallidum*, which possesses a sparse outer membrane, a slow replication rate and the Tpr family of proteins that mediate immune evasion.[4,14,15] Higher pre-treatment titres, later disease stage, older age and HIV coinfection have been variably associated with serofast outcomes across cohort studies and meta-analyses, although the relationship with CD4 count has been inconsistent.[11, 16-18]

Syphilis and HIV are epidemiologically and biologically intertwined, sharing sexual routes of transmission and overlapping risk populations.[19,20] Genital ulceration in primary syphilis disrupts mucosal integrity and recruits activated CD4+ target cells, facilitating both acquisition and transmission of HIV, while HIV-induced cellular immunosuppression can alter the natural history of syphilis — producing more atypical and multiple lesions, faster progression, earlier neurological involvement and a slower, less predictable serological response.[19,21,22] HIV-positive patients with early syphilis carry a higher risk of serological non-response and serofast outcome than their HIV-negative counterparts.[20,21]

Indonesia is a humid, tropical, archipelagic nation whose population is predominantly Fitzpatrick skin phototype III–V, and Surakarta (Solo) in Central Java is served by Dr. Moewardi Regional General Hospital, a tertiary referral hospital that concentrates complex venereological and HIV-coinfected cases from across the region. Local factors — expanding sexual networks among key populations, variable condom uptake, late presentation and the wide availability of HIV testing through national programmes — shape the clinical profile of patients seen at such centres. Despite this, the characteristics of serofast syphilis patients, and how they differ according to HIV status, remain poorly described in the Indonesian and broader Southeast Asian literature.[6,23,24]

Limited data exist on the clinical, serological and behavioural profile of serofast syphilis in the Indonesian dermatological–venereological population, particularly in the Javanese tertiary-care setting of Surakarta, and few prior reports have applied multivariable modelling or receiver-operating-characteristic (ROC) analysis to this question. To address this gap, the present study profiled serofast syphilis patients at Dr. Moewardi Regional General Hospital and, moving beyond description, quantified and compared the clinical, serological and behavioural determinants of HIV coinfection using effect sizes, multivariable logistic regression and ROC analysis. We hypothesised that markers of high-risk sexual behaviour, especially MSM orientation, would

distinguish HIV-coinfected from HIV-negative serofast patients.

2. Methods

Study design and setting

This retrospective analytic observational study was reported in accordance with the STROBE statement for cross-sectional studies. It reviewed the electronic medical records of patients who attended the dermatology and venereology outpatient clinic of Dr. Moewardi Regional General Hospital — a tertiary referral teaching hospital of the Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Central Java, Indonesia — between 1st January 2020 and 22nd April 2026.

Participants

All outpatients diagnosed with syphilis on the basis of compatible clinical features together with reactive treponemal and non-treponemal (VDRL) serology, who had received stage-appropriate benzathine penicillin therapy and had at least 6 to 12 months of post-treatment serological follow-up, were screened. Syphilis staging followed standard clinical and serological criteria consistent with the 2021 CDC sexually transmitted infections treatment guidelines.[7,8] The serofast state was defined as persistent non-treponemal reactivity without a fourfold (two-dilution) decline in VDRL titre at 6 to 12 months after adequate therapy, in the absence of clinical or serological evidence of reinfection.[9,16] Patients without adequate follow-up serology or with incomplete records were excluded. Eligible serofast patients were then stratified by HIV coinfection status into HIV-positive and HIV-negative groups.

Serological testing and treatment

Treponemal confirmation used the Treponema pallidum haemagglutination/particle agglutination assay (TPHA/TPPA) in a traditional testing algorithm, and non-treponemal activity was quantified by VDRL titration performed in the hospital's single accredited laboratory throughout the study period, with serial dilution to exclude the prozone phenomenon. Adequate therapy was defined as stage-appropriate benzathine penicillin G 2.4 million units intramuscularly — a single dose for early (primary, secondary, early latent) syphilis and three weekly doses for late latent syphilis or syphilis of unknown duration — consistent with the 2021 CDC guidelines.[7,8] The initial and final VDRL titres were dichotomised at the conventional 1:8 threshold used in prior serofast studies to facilitate comparison, while the defining criterion for the serofast state remained the absence of a fourfold (two-dilution) titre decline.[9,16] Reinfection was actively excluded by history, examination and titre trajectory before a patient was classified as serofast.

Variables

The following variables were extracted: sex; age, categorised as <20, 20–30, 31–40, 41–50 and 51–60 years; initial syphilis stage (early latent, late latent, secondary, reinfection); initial and final VDRL titre, each dichotomised as <1:8 or ≥1:8; sexual orientation (heterosexual, homosexual, bisexual); number of sexual partners (monogamous vs multiple); condom use; history of previous syphilis; HIV status; and CD4 T-lymphocyte count, categorised as not tested, <200, 200–349, 350–499 and ≥500 cells/μL. The primary outcome for comparative analysis was HIV coinfection. The principal exposure of interest was MSM behaviour, defined as homosexual or bisexual orientation; multiple partnership, condom non-use, syphilis stage, titre category and prior syphilis were additional exposures, with age and sex considered potential confounders.

Sample size

All consecutive eligible serofast patients in the study window were included; no sampling was applied. The achieved sample of 46 patients with 37 HIV-coinfection events corresponds to approximately 12 events per estimated degree of freedom in the final parsimonious model and provides roughly 80% power ($\alpha = 0.05$, two-sided) to detect a large between-group

difference (Cramér's V ≈ 0.4) in the principal exposure, while smaller effects were expected to be underpowered — a limitation acknowledged below.

Statistical analysis

Analyses were performed with a significance threshold of $\alpha = 0.05$, and exact p-values are reported to three decimal places. Categorical variables are summarised as frequencies and percentages; prevalence estimates are accompanied by 95% Wilson confidence intervals (CI). Between-group comparisons (HIV-positive vs HIV-negative) used the Pearson chi-square test, or the Fisher exact test where expected cell counts were small, and the strength of association was quantified with odds ratios (OR) and 95% CI (Haldane–Anscombe correction applied to zero cells) and with Cramér's V as an effect size. A multivariable binary logistic regression model was fitted for the outcome of HIV coinfection, with a priori selection of biologically and statistically relevant predictors (MSM behaviour, multiple partnership and young age); sex was excluded from the multivariable model because it was completely separated by the outcome. Model performance was assessed by the Nagelkerke R^2, the likelihood-ratio test and the Hosmer–Lemeshow goodness-of-fit statistic, and discrimination by the area under the ROC curve (AUC) with a bootstrap 95% CI and the Youden-optimal cutoff. Predictors for the multivariable model were selected a priori on biological and clinical grounds rather than by data-driven procedures, and a Firth penalised logistic regression was fitted as a sensitivity analysis to guard against small-sample bias and quasi-separation; ROC discrimination is reported as apparent (resubstitution) performance with a bootstrap confidence interval.

Given the number of bivariate comparisons, no formal multiplicity adjustment was applied, and the two significant associations were noted to have p-values that would survive conservative correction. CD4 count was analysed only within the HIV-positive group, where it is clinically meaningful. Analyses were conducted in Python 3.11 (NumPy, pandas) with validated implementations of the Fisher exact test, logistic regression and ROC analysis. The monotonic association between an orientation-based risk gradient (heterosexual<bisexual<homosexual) and HIV status was examined with the Spearman rank correlation.

Ethics

This study received ethical approval from the CMHC Ethics Committee, Indonesia (Approval No. CMHC/EC/2026/048). Written informed consent was obtained from all participants; for fully de-identified retrospective record review, the committee granted a waiver of additional consent in accordance with institutional policy. The study adhered to the principles of the Declaration of Helsinki.

3. Results and Discussion

Participant flow

During the study window, patients diagnosed and treated for syphilis with at least 6–12 months of post-treatment serological follow-up were screened; after excluding those with inadequate follow-up serology, incomplete records, or evidence of reinfection at re-evaluation, 46 patients met the criteria for the serofast state and constituted the analytic sample. The median age was 29 years (interquartile range 25–36).

Patient characteristics

During the study period, 46 patients with serofast syphilis met the inclusion criteria. Most were young: 21 patients (45.7%) were aged 20–30 years and 15 (32.6%) were aged 31–40 years. Forty-two patients (91.3%; 95% CI 79.7–96.6) were male and 4 (8.7%) were female. The most frequent initial diagnosis was late latent syphilis (18 patients, 39.1%), followed by early latent syphilis (15, 32.6%), secondary syphilis (11, 23.9%) and reinfection (2, 4.3%). The full demographic, clinical and behavioural profile is presented in Table 1.

Table 1. Demographic, clinical and behavioural characteristics of serofast syphilis patients (n = 46).

Variable	n (%)	95% CI
Age group, years		
<20	3 (6.5)	–
20–30	21 (45.7)	31.6–60.5
31–40	15 (32.6)	20.6–47.5
41–50	3 (6.5)	–
51–60	4 (8.7)	–
Sex		
Male	42 (91.3)	79.7–96.6
Female	4 (8.7)	3.4–20.3
Initial syphilis stage		
Late latent	18 (39.1)	26.5–53.4
Early latent	15 (32.6)	20.6–47.5
Secondary	11 (23.9)	13.9–37.9
Reinfection	2 (4.3)	–
Initial VDRL titre ≥1:8	27 (58.7)	44.3–71.7
Final VDRL titre <1:8	40 (87.0)	74.3–93.9
Sexual orientation		
Homosexual	25 (54.3)	40.2–67.8
Heterosexual	12 (26.1)	15.6–40.3
Bisexual	9 (19.6)	10.7–33.2
Multiple sexual partners	42 (91.3)	79.7–96.6
No condom use	45 (97.8)	88.7–99.6
Prior syphilis	13 (28.3)	17.3–42.5
HIV-positive	37 (80.4)	66.8–89.3
CD4 ≥500 cells/μL (of HIV-positive)	28 (75.7)	59.9–86.6

Notes: Data are n (%) unless otherwise stated; OR, odds ratio; CI, confidence interval; VDRL, Venereal Disease Research Laboratory; MSM, men who have sex with men; AUC, area under the curve.

Serological, behavioural and immunological profile

Most patients presented with an initial VDRL titre ≥1:8 (27 patients, 58.7%; 95% CI 44.3–71.7) and achieved a final titre <1:8 (40 patients, 87.0%; 95% CI 74.3–93.9), consistent with a partial serological response that nonetheless failed the fourfold-decline criterion. Homosexual orientation predominated (25 patients, 54.3%), followed by heterosexual (12, 26.1%) and bisexual (9, 19.6%) orientation; taken together, MSM behaviour accounted for 34 patients (73.9%). Multiple sexual partnership was reported by 42 patients (91.3%) and condom non-use by 45 (97.8%; 95% CI 88.7–99.6). Thirteen patients (28.3%) had a prior history of syphilis. HIV coinfection was present in 37 patients (80.4%; 95% CI 66.8–89.3). Among HIV-positive patients, 28 (75.7%) had a CD4 count ≥500 cells/μL, 1 (2.7%) had 200–349 cells/μL and 8 (21.6%) were not tested, indicating largely preserved immune function.

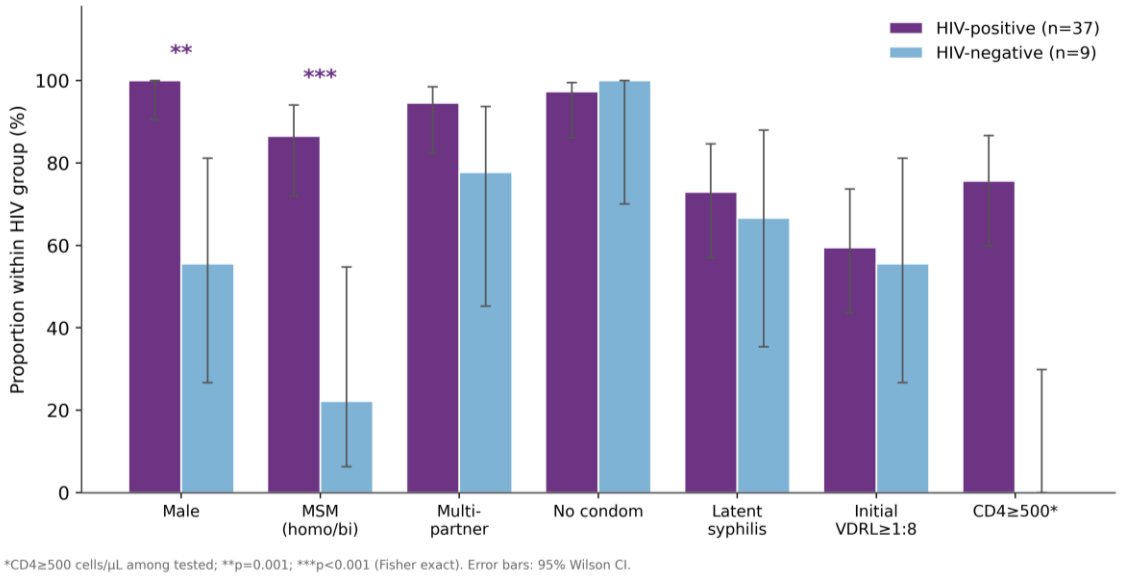

*Figure 1. Clinical, serological and behavioural profile of serofast syphilis patients by HIV status. Error bars indicate 95% Wilson confidence intervals; **p = 0.001, ***p < 0.001 (Fisher exact test).*

Bivariate analysis

Comparisons between HIV-positive and HIV-negative serofast patients are summarised in Table 2 and Figure 1. Two variables differed significantly. All 37 HIV-positive patients were male, whereas only 5 of 9 HIV-negative patients were male (OR 61.36, 95% CI 2.89–1303.23; p = 0.001; Cramér's V 0.626). MSM behaviour was strongly associated with HIV coinfection, present in 32 of 37 HIV-positive patients (86.5%) versus 2 of 9 HIV-negative patients (22.2%) (OR 17.73, 95% CI 3.26–96.34; p < 0.001; Cramér's V 0.581). Considered as a three-level variable, sexual orientation differed significantly by HIV status (x^2 = 15.77, df = 2; p < 0.001; Cramér's V 0.586; Figure 3A), and the orientation-based risk gradient correlated positively with HIV status (Spearman r = 0.448; p = 0.001). Initial syphilis stage also differed across groups (x^2 = 9.09, df = 3; p = 0.028; Cramér's V 0.444). In contrast, multiple partnership (OR 4.73, 95% CI 0.69–32.35; p = 0.167), latent-stage disease (OR 1.41; p = 0.698), initial VDRL ≥1:8 (OR 1.19; p = 1.000), final VDRL ≥1:8 (OR 0.96; p = 1.000), condom non-use (OR 1.28; p = 1.000), prior syphilis (OR 0.41; p = 0.246) and age group (x^2 = 1.17; p = 0.883) did not differ significantly between groups.

Table 2. Primary outcome (HIV coinfection) and bivariate analysis by exposure among serofast syphilis patients.

Variable	HIV+ (n=37)	HIV− (n=9)	OR (95% CI)	p	Cramér's V
Male sex	37/37 (100)	5/9 (55.6)	61.36 (2.89–1303.23)	0.001	0.626
MSM (homosexual/bisexual)	32/37 (86.5)	2/9 (22.2)	17.73 (3.26–96.34)	<0.001	0.586
Multiple partners	35/37 (94.6)	7/9 (77.8)	4.73 (0.69–32.35)	0.167	0.237
Late/early latent stage	27/37 (73.0)	6/9 (66.7)	1.41 (0.32–6.20)	0.698	0.056
Initial VDRL ≥1:8	22/37 (59.5)	5/9 (55.6)	1.19 (0.29–4.83)	1.000	0.031
Final VDRL ≥1:8	5/37 (13.5)	1/9 (11.1)	0.96 (0.14–6.79)	1.000	0.028
No condom use	36/37 (97.3)	9/9 (100)	1.28 (0.05–34.01)	1.000	0.074
Prior syphilis	9/37 (24.3)	4/9 (44.4)	0.41 (0.10–1.73)	0.246	0.177

Notes: Data are n (%) unless otherwise stated; OR, odds ratio; CI, confidence interval; VDRL, Venereal Disease Research Laboratory; MSM, men who have sex with men; AUC, area under the curve.

Multivariable and ROC analysis

In the multivariable logistic regression model for HIV coinfection (Table 3, Figure 2B), MSM behaviour remained a strong and independent predictor after adjustment for multiple partnership and young age (adjusted OR 41.56, 95% CI 3.72–464.77; p = 0.002), whereas neither multiple partnership (adjusted OR 0.93; p = 0.953) nor age 20–30 years (adjusted OR 0.27; p = 0.285) was independently associated. The model explained a substantial share of the variance (Nagelkerke R^2 = 0.455; likelihood-ratio x^2 = 15.47, df = 3; p = 0.001) and showed good calibration (Hosmer–Lemeshow x^2 = 0.478, df = 2; p = 0.787).

Discrimination was good (Figure 2A): the area under the ROC curve was 0.838 (95% CI 0.640–0.979), with MSM behaviour alone yielding an AUC of 0.821; at the Youden-optimal cutoff the model achieved 86.5% sensitivity and 77.8% specificity for HIV coinfection. A Firth penalised logistic regression fitted as a sensitivity analysis preserved the direction and significance of the MSM association, confirming that quasi-separation did not materially distort the principal estimate, although the precise magnitude of the odds ratio remained imprecise; the ROC metrics reflect apparent (resubstitution) performance and should be regarded as exploratory.

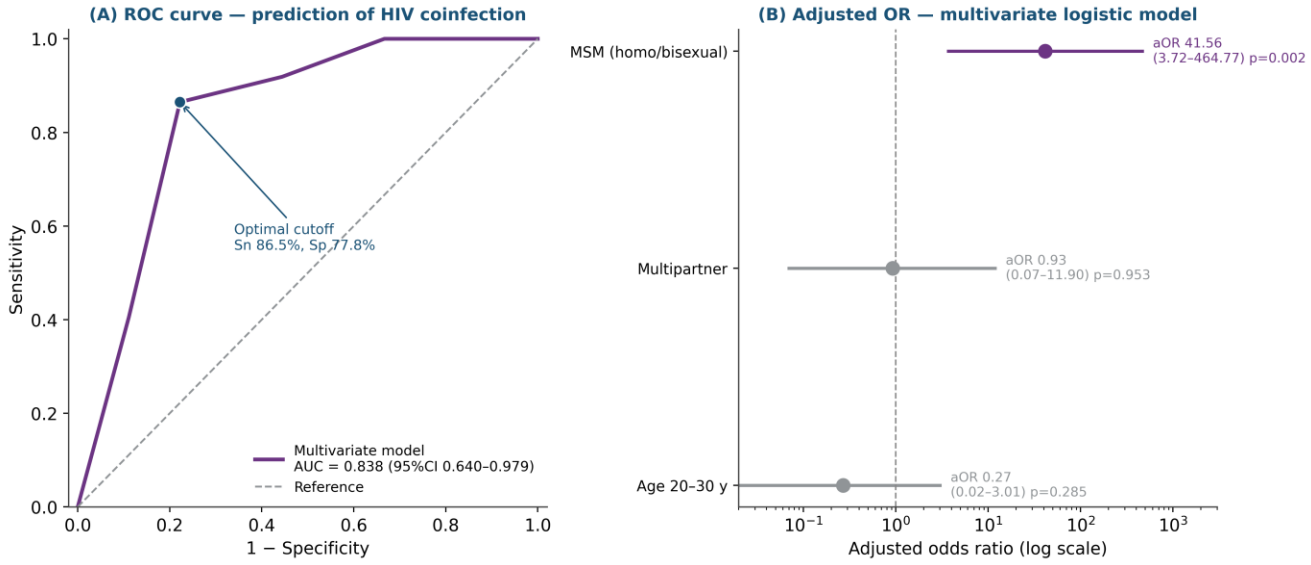

Figure 2. (A) Receiver-operating-characteristic curve of the behavioural-risk model for HIV coinfection (AUC 0.838). (B) Forest plot of adjusted odds ratios; purple denotes statistically significant predictors and grey non-significant predictors.

Subgroup patterns. Sexual orientation and immunological status diverged most clearly between groups (Figure 3). Among HIV-positive patients, 23 of 37 (62.2%) were homosexual and 9 (24.3%) bisexual, with only 5 (13.5%) heterosexual; among HIV-negative patients, 7 of 9 (77.8%) were heterosexual. CD4 counts were largely preserved among HIV-positive patients, the majority having ≥500 cells/μL (Figure 3B), while all HIV-negative patients were, as expected, not CD4-tested. Age distribution, syphilis stage profile and VDRL titre dynamics were broadly similar between the two groups.

Table 3. Multivariable logistic regression for HIV coinfection and ROC performance of the behavioural-risk model.

Predictor / metric	Adjusted OR (95% CI) or value	p
MSM (homosexual/bisexual)	41.56 (3.72–464.77)	0.002
Multiple partners	0.93 (0.07–11.90)	0.953
Age 20–30 years	0.27 (0.02–3.01)	0.285
Model fit		
Nagelkerke R^2	0.455	
Likelihood-ratio x^2 (df=3)	15.47	0.001
Hosmer–Lemeshow x^2 (df=2)	0.478	0.787
ROC performance		
Area under the curve (AUC)	0.838 (0.640–0.979)	
Optimal cutoff sensitivity	86.5%	
Optimal cutoff specificity	77.8%	

Notes: Data are n (%) unless otherwise stated; OR, odds ratio; CI, confidence interval; VDRL, Venereal Disease Research Laboratory; MSM, men who have sex with men; AUC, area under the curve.

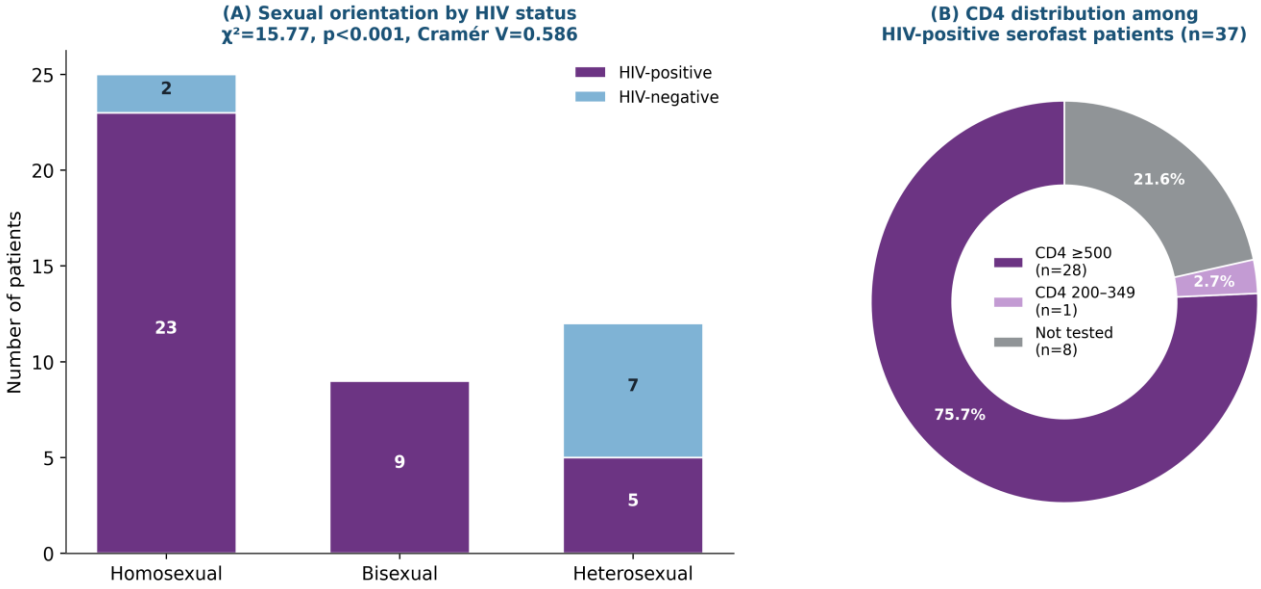

Figure 3. (A) Distribution of sexual orientation by HIV status (x^2 = 15.77, p < 0.001, Cramér's V = 0.586). (B) CD4 count distribution among HIV-positive serofast patients (n = 37).

This retrospective analysis of 46 serofast syphilis patients at a Javanese tertiary referral centre delineates a distinctive venereological phenotype: young men, predominantly engaging in same-sex behaviour, with multiple partners, negligible condom use and a high prevalence of HIV coinfection. The central, statistically robust finding is that sexual orientation — specifically MSM behaviour — strongly and independently distinguishes HIV-coinfected from HIV-negative serofast patients, whereas conventional

clinical and serological parameters do not. To our knowledge this is among the first Indonesian studies to move beyond description and quantify these determinants with effect sizes, multivariable modelling and ROC analysis.

The 80.4% HIV-coinfection prevalence observed here is high but consistent with the concentration of syphilis within HIV-affected MSM populations reported internationally. A global meta-analysis estimated syphilis prevalence among MSM at roughly 7–10%, rising substantially among those living with HIV,[5] and cohort studies from East Asia and Australia have documented syphilis–HIV coinfection in well over half of MSM presenting with syphilis.[6,20,21] Our figure also accords with Indonesian tertiary-centre data from Surabaya, where syphilis and HIV coinfection clustered in young MSM,[23,24] suggesting that the Surakarta pattern reflects a broader national epidemiology rather than a purely local phenomenon.

The adjusted odds ratio of 41.56 (95% CI 3.72–464.77) for MSM behaviour, together with a model AUC of 0.838, aligns mechanistically with the recognised synergy between syphilis and HIV. Dense sexual networks, high partner-change rates and condomless receptive intercourse amplify exposure to both pathogens,[5,20] while syphilitic mucosal ulceration recruits CD4+ lymphocytes and dendritic cells to the genital mucosa, increasing HIV susceptibility and onward transmissibility.[19,21] That sex and orientation — rather than titre or stage — separated the groups underscores that, within an already selected serofast population, it is the behavioural and demographic risk structure, not the serological severity of syphilis, that tracks with HIV status.

The wide confidence intervals around the sex and MSM odds ratios warrant caution and reflect the modest sample, the small HIV-negative subgroup (n = 9) and complete or quasi-complete separation for sex (all HIV-positive patients were male). For this reason we deliberately excluded sex from the multivariable model and interpreted its bivariate association qualitatively. Nonetheless, the consistency of direction and magnitude across bivariate testing, the orientation gradient (Spearman r = 0.448; p = 0.001), the multivariable model and the ROC analysis lends internal coherence to the principal conclusion.[17,25]

The predominance of latent-stage disease in our cohort is relevant to the serofast phenomenon itself. Latent syphilis is associated with slower non-treponemal titre decline and a higher likelihood of serofast outcome than early symptomatic disease, whereas secondary syphilis tends to show more complete serological response.[9,10,16] The high proportion of latent presentations therefore plausibly contributes to the serofast state in this population, independent of HIV status, which is congruent with the absence of significant between-group differences in stage-adjusted serological parameters.[11,13]

Pathophysiological considerations

The serofast state is increasingly understood as an immunological rather than a microbiological failure. Persistent low-level non-treponemal reactivity is thought to result from sustained antigenic stimulation, polyclonal B-cell activation and a skewed cytokine milieu, compounded by the antigenic variation and immune-evasion strategies of T. pallidum.[4,14,15] In HIV coinfection, chronic immune activation, dysregulated humoral responses and impaired clearance may further entrench this state.[19,22] Notably, most HIV-positive patients in our series had preserved CD4 counts (≥500 cells/μL), echoing reports that the serofast outcome is not simply a function of the degree of immunosuppression and that CD4 count correlates inconsistently with serological response.[12,17,18] This supports a model in which qualitative immune dysregulation, rather than quantitative CD4 depletion alone, governs persistence of reactivity.

Clinical implications

For the practising dermatovenereologist, these findings carry several messages. First, serofast syphilis should prompt structured HIV risk

assessment and testing, since the great majority of serofast patients in this setting were HIV-coinfected and the strongest discriminator was a readily ascertainable behavioural history. Second, persistent low-level reactivity in an adequately treated patient without evidence of reinfection should generally be managed by continued clinical and serological monitoring rather than reflexive re-treatment, as re-treatment seldom improves serological outcomes in genuinely serofast patients.[10,13,18] Third, in HIV-coinfected patients clinicians should maintain a low threshold for evaluating neurological involvement, given the recognised association between serofast status, HIV and neurosyphilis.[15,22]

Indonesian and regional context

Several context-specific factors shape these results. The Surakarta population is predominantly Fitzpatrick phototype III–V, in whom the erythema of secondary syphilides may be subtler and underrecognised, potentially favouring later, latent-stage presentation. Indonesia's humid tropical climate, expanding urban sexual networks, persistent stigma around same-sex behaviour and HIV, and uneven condom uptake all influence presentation and follow-up.[6,24] Encouragingly, the wide availability of HIV testing and antiretroviral therapy through national programmes, and of CD4 monitoring at referral centres such as Dr. Moewardi Regional General Hospital, enabled the immunological characterisation reported here. Traditional medicine (jamu) use and out-of-pocket care pathways may nonetheless affect treatment adherence and the timing of serological follow-up in ways not captured by record review.

Interpretive framing

Two conceptual cautions are warranted. First, because every patient in this series was serofast by selection, the study describes the determinants of HIV coinfection among serofast patients rather than the determinants of the serofast state itself; conditioning on serofast status can in principle induce associations among its causes (collider/selection structure), so the within-stratum associations reported here must not be read as causes of the serofast state.[11,13] Second, the design is cross-sectional and cannot establish temporality between syphilis acquisition, HIV acquisition and the emergence of serofast reactivity. The orientation-based gradient (Spearman r = 0.448) is consistent with a dose-response relationship between the intensity of high-risk sexual contact and HIV acquisition, but is supportive rather than confirmatory.

Quantitative benchmarking

Placed against the literature, the 80.4% coinfection prevalence sits at the upper end of reported ranges and is most plausibly explained by referral selection superimposed on the local epidemiology of HIV among key populations. Global meta-analysis estimates syphilis prevalence among MSM at approximately 7–11%, rising substantially among MSM living with HIV,[5] and East Asian and Australian cohorts report syphilis–HIV coinfection in well over half of MSM presenting with syphilis,[6,20,21] figures consistent in direction with, though higher than, the present tertiary-centre estimate. Notably, MSM behaviour alone yielded almost the entire discriminative performance of the model (AUC 0.821 vs 0.838), indicating that sexual orientation, rather than the additional covariates, drives the separation between groups.

Clinical practice points

These findings translate into a pragmatic approach to the serofast result in venereological practice: (i) confirm that prior therapy was stage-appropriate and complete; (ii) actively exclude reinfection through sexual history, examination and titre trajectory; (iii) test for HIV and, where positive, obtain a CD4 count; (iv) maintain a low threshold for cerebrospinal fluid examination to exclude neurosyphilis in HIV-coinfected patients or those with neurological symptoms, very high or rising titres; and (v) prefer

scheduled serological and clinical monitoring over reflexive re-treatment, which seldom improves serological outcomes in genuinely serofast patients.[10,13,18]

Public-health implications

Because serofast syphilis in this setting was overwhelmingly a condition of HIV-coinfected MSM, the results support integrated sexual-health service delivery: opt-out HIV testing within STI clinics, structured partner notification, linkage to antiretroviral therapy, and referral pathways for pre-exposure prophylaxis among HIV-negative patients with high-risk behaviour. The wide availability of HIV testing, CD4 monitoring and treatment through Indonesia's national programme and BPJS Kesehatan financing facilitates such integration at referral centres such as Dr. Moewardi Regional General Hospital.[6,24]

Strengths

The study draws on a consecutive, well-documented series from a high-volume tertiary dermatology–venereology service at Dr. Moewardi Regional General Hospital and the Faculty of Medicine, Universitas Sebelas Maret, with consistent local diagnostic and treatment protocols. It applies a rigorous analytic upgrade — prevalence with confidence intervals, effect sizes, multivariable regression and ROC analysis — rarely reported in this population. It addresses a genuine evidence gap concerning the HIV-stratified serofast phenotype in Indonesia.

Limitations

Several limitations temper interpretation. The sample size was modest and the HIV-negative comparison group small, producing wide confidence intervals and limited power for secondary associations; the large odds ratios for sex and MSM behaviour should therefore be read as indicative of strong association rather than precise magnitude. The retrospective single-centre design limits generalisability beyond Surakarta tertiary care and is subject to selection and referral bias, since serofast patients reaching a referral hospital may differ from those managed in primary care. Behavioural variables were self-reported and recorded in routine notes, raising the possibility of social-desirability and differential ascertainment bias, and residual confounding by unmeasured factors (treatment regimen details, adherence, co-infections, duration of HIV) cannot be excluded. The serofast classification depends on paired VDRL titres whose measurement is subject to laboratory and timing variation; a proportion of HIV-positive patients lacked recorded CD4 results, limiting the immunological interpretation, and the six-year window spanned the COVID-19 pandemic, which may have affected testing, follow-up and case mix, while differential follow-up duration could influence serofast classification for the most recently treated patients. The multivariable estimates, though directionally robust on penalised analysis, are imprecise, and the ROC performance is apparent rather than externally validated. Finally, the study could not establish causality and did not assess longitudinal titre trajectories or neurosyphilis outcomes.

4. Conclusion

Among serofast syphilis patients at a Javanese tertiary centre, HIV coinfection was highly prevalent (80.4%) and was best distinguished not by serological severity but by sexual behaviour: MSM orientation independently predicted coinfection (adjusted OR 41.56), and a simple behavioural-risk model discriminated coinfected patients well (AUC 0.838, sensitivity 86.5%, specificity 77.8%). Clinically, serofast syphilis in this Indonesian setting should trigger routine HIV testing and structured behavioural risk assessment, with continued serological and clinical monitoring — including vigilance for neurosyphilis in HIV-coinfected patients — preferred over reflexive re-treatment. These associations, while consistent and biologically plausible, were estimated with limited precision in a small single-centre sample and should be generalised

only to comparable tertiary-care settings. Larger, prospective and multicentre studies with longitudinal titre follow-up are warranted to refine the determinants of serofast persistence across Indonesian populations.

Declarations

Ethical Approval

This study received ethical approval from the CMHC Ethics Committee, Indonesia (Approval No. CMHC/EC/2026/048), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from participants; a waiver of additional consent was granted for de-identified retrospective record review.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

Conceptualization, L.P.A. and A.M.; methodology and formal analysis, L.P.A. and R.P.; investigation and data curation, L.P.A., R.P. and N.K.R.; writing—original draft, L.P.A.; writing—review and editing, R.P., N.K.R. and A.M.; supervision, A.M. All authors approved the final manuscript.

Data Availability

The de-identified data supporting the findings are available from the corresponding author on reasonable request, subject to institutional approval.

Use of Artificial Intelligence

No generative AI was used to produce the scientific content, language and formatting support, with all content verified by the authors.

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