

Evaluating the Serofast State in Syphilis: A Study of Clinical Characteristics, Immunological Markers, and HIV Status

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ABSTRACT

Syphilis remains a significant global health burden, particularly among high-risk populations such as men who have sex with men (MSM). A major challenge in management is the serofast state, where patients fail to achieve serological cure despite adequate treatment. The immunological mechanisms driving this, especially in the context of HIV co-infection, remain unclear. This study aims to evaluate clinical and immunological factors associated with serofast status versus serological cure. A retrospective cohort study was conducted on 40 patients diagnosed with syphilis (early latent, late latent, or secondary). Data on demographics, HIV status, CD4/CD8 counts, and pre- and post-treatment VDRL titers were analyzed. Bivariate and multivariate logistic regression analyses were performed to identify predictors of the serofast outcome. The cohort was predominantly males (90.0%) and unmarried (80.0%). HIV co-infection was identified as the sole independent predictor of the serofast state (aOR = 10.94; 95% CI: 1.72-69.65; p=0.011). While post-treatment VDRL titers significantly decreased in the total cohort, the serofast group retained significantly higher antibody levels compared to the serological cure group (p<0.001). However, no statistically significant differences were found in CD4 counts, CD8 counts, or CD4/CD8 ratios between the two groups. HIV co-infection is a strong predictor of the serofast state in syphilis patients. The lack of significant differences in quantitative cellular immune markers suggests that the persistence of antibodies may be driven by functional immune dysregulation rather than absolute T-cell depletion. These findings emphasize the need for vigilant serological monitoring in HIV-syphilis co-infected individuals.

Keywords: CD4/CD8 ratio; HIV Co-infection; Serofast; Serological Cure; Syphilis

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INTRODUCTION

Syphilis, a systemic infection caused by the spirochete *Treponema pallidum*, remains a formidable global public health challenge. Despite the availability of effective antibiotic therapy, the infection has experienced a marked resurgence since the early 2000s, with rising incidence rates observed globally, particularly in North America, Europe, and Asia (Rana et al., 2019; Kidd et al., 2018; Zheng et al., 2024). This resurgence is disproportionately concentrated among men who have sex with men (MSM), driven by a complex interplay of behavioral factors such as condomless sex and multiple sexual partners, as well as structural barriers to healthcare (Kidd et al., 2018; Novak et al., 2018).

The clinical management of syphilis relies heavily on serological monitoring to confirm treatment success. A serological cure is generally defined as a four-fold decline in non-treponemal antibody titers following therapy. However, a significant subset of patients estimated at between 20% and 40%, fails to achieve this decline, persisting in a state known as serofast despite adequate treatment and the absence of clinical reinfection (Zeng et al., 2025;

Zhang et al., 2017). The pathogenesis of the serofast state remains a clinical conundrum. Recent literature suggests it is associated with immunological dysregulation, specific cytokine profiles, and host genetic factors, yet the precise mechanisms driving this persistence are not fully understood (Pastuszczak et al., 2017; Kaminiów et al., 2025; Cao et al., 2024).

The challenge of managing serofast syphilis is significantly amplified in the context of HIV co-infection. Syphilis and HIV form a dangerous syndemic; syphilis facilitates HIV acquisition and transmission via mucosal disruption and immune modulation, while HIV co-infection alters the natural history and serological response of syphilis (Puspawati et al., 2025; Tansey et al., 2018). Co-infected patients often exhibit atypical serological responses, including higher rates of serofast status, false negatives, or delayed serological cure (Zeng et al., 2025). Furthermore, syphilis co-infection can negatively impact HIV management by inducing transient declines in CD4 counts, altering the CD4/CD8 ratio, and increasing viral loads, thereby complicating the interpretation of immune recovery (Fan et al., 2021; Muccini et al., 2021).

Despite the established epidemiological link between HIV and serofast syphilis, there is a lack of consensus regarding the specific clinical and immunological predictors that distinguish patients who achieve serological cure from those who remain serofast (Patel et al., 2025). While low baseline titers and HIV status are known risk factors, the roles of specific cellular immunity markers such as CD4 and CD8 T-cell counts and the dynamics of VDRL titers in this process require further elucidation (Zhang et al., 2017).

The urgency of this research is underscored by several critical factors. First, the rising incidence of syphilis globally and in Indonesia, particularly among key populations, demands improved understanding of treatment outcomes to optimize clinical management. Second, the high prevalence of HIV co-infection in syphilis-affected populations creates complex clinical scenarios where standard treatment algorithms may not adequately predict outcomes. Third, the serofast state creates clinical uncertainty that may lead to unnecessary retreatment, patient anxiety, and continued risk of transmission if persistent infection is actually present. Fourth, understanding the immunological mechanisms underlying the serofast state could inform the development of novel therapeutic approaches or biomarkers for predicting treatment response. Fifth, in resource-limited settings where sophisticated diagnostic testing may be unavailable, identifying simple clinical predictors of serofast outcomes could guide treatment and monitoring strategies.

Given the complexities of syphilis-HIV co-infection and the ambiguity surrounding immune markers in treatment outcomes, this study aims to evaluate the differences in clinical and immunological parameters specifically HIV status, CD4 and CD8 counts, and VDRL titer dynamics between patients achieving serological cure and those remaining in a serofast state. Understanding these factors is crucial for optimizing the management of syphilis, particularly in high-risk populations.

RESEARCH METHODS

Study Design

This was a retrospective observational analytic study conducted using secondary data derived exclusively from medical records. The study aimed to evaluate the differences in clinical and immunological profiles between patients with serofast syphilis and those achieving

serological cure. Data extraction was performed at the Medical Record Unit of the Dermatology and Venereology Polyclinic at Dr. Moewardi General Hospital, Surakarta. The data collection period was carried out from January 2022 to December 2024, retrieving relevant patient history and laboratory results from the hospital registry.

Study Population and Sampling

The study population consisted of all patients diagnosed with syphilis whose data were available in the medical records of Dr. Moewardi General Hospital. The subjects were categorized into two groups based on their recorded treatment outcomes, the serofast syphilis group and the serological cure group. A total sampling technique was employed, whereby all medical records meeting the inclusion and exclusion criteria within the study period were included in the analysis. No direct patient interaction or primary sample collection was performed for this study.

Eligibility Criteria

The inclusion criteria comprised medical records of patients diagnosed with syphilis across all stages. To be included, records were required to have documented VDRL titer examinations both before and at least six months after receiving adequate, stage-appropriate therapy. Only medical records with complete clinical data regarding diagnosis, treatment, and follow-up were included in the study.

Statistical Analysis

Data analysis was performed using SPSS software. Descriptive statistics were used to present baseline characteristics, with continuous variables expressed as means and standard deviations or medians and mean ranks depending on normality, and categorical variables expressed as frequencies and percentages. The normality of data distribution was assessed to determine appropriate hypothesis testing. Bivariate analysis was conducted using the Chi-Square test or Fisher's Exact test for categorical variables. For continuous variables, the Independent Samples T-test was used for normally distributed data, while the Mann-Whitney U test was employed for non-normally distributed data. To evaluate the effectiveness of treatment within the cohort, the Wilcoxon Signed Rank test was used to compare pre-treatment and post-treatment VDRL titers. Finally, binary logistic regression was performed to identify independent risk factors associated with the serofast outcome. A p-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

A total of 40 subjects were included in this study based on medical record review. The demographic analysis (Table 1) shows that the majority of subjects were in the age group of 21-30 years (50.0%) and were predominantly male (90.0%). Regarding occupation, 72.5% of the subjects were employed. The clinical distribution of syphilis stages varied, with late latent syphilis being the most common (37.5%), followed by secondary syphilis (35.0%) and early latent syphilis (27.5%). Regarding sexual orientation and marital status (Table 2), all homosexual subjects (n=24) were unmarried, whereas the majority of bisexual subjects (60%) were married.

Table 1. Baseline Characteristics of Study Subjects

Variable	Category	Frequency (n)	Percentage (%)
Age Group	< 20 Years	5	12.5

	21-30 Years	20	50.0
	31-40 Years	12	30.0
	> 40 Years	3	7.5
Gender	Male	36	90.0
	Female	4	10.0
Occupation	Unemployed / Student	11	27.5
	Employed	29	72.5
Syphilis Stage	Early Latent	11	27.5
	Late Latent	15	37.5
	Secondary	14	35.0

Table 2. Sexual Orientation and Marital Status

Sexual Orientation	Married (n=8)	Unmarried (n=32)	Total (n=40)
Bisexual	3 (60.0%)	2 (40.0%)	5
Heterosexual	5 (45.5%)	6 (54.5%)	11
Homosexual	0 (0.0%)	24 (100.0%)	24

The treatment outcome was categorized into serological cure (n=13) and the serofast group (n=27). Bivariate analysis (Table 3) using Fisher's Exact Test indicated that age group (p=0.599), marital status (p=0.521), gender (p=0.608), and syphilis stage (p=0.329) were not significantly associated with the treatment outcome.

However, HIV status showed a marginal significance (p=0.052). Among those with a serofast outcome, a substantially higher proportion were HIV positive (77.8%) compared to the serological cure group (46.2%). The unadjusted Odds Ratio suggested that HIV-negative individuals were more likely to achieve serological cure, though this crossed the threshold of statistical significance in the bivariate model.

Table 3. Bivariate Analysis of Factors Associated with Treatment Outcome (Serological cure vs. Serofast)

Variable	Category	Serological cure (n=13)	Serofast (n=27)	OR (95% CI)	P-value
Age	≤ 30 Years	8 (32.0%)	17 (68.0%)	0.94 (0.24 - 3.68)	0.599
	> 30 Years	5 (33.3%)	10 (66.7%)		
Marital Status	Married	3 (37.5%)	5 (62.5%)	1.32 (0.26 - 6.64)	0.521
	Unmarried	10 (31.3%)	22 (68.8%)		
Gender	Male	12 (33.3%)	24 (66.7%)	1.50 (0.14 - 16.0)	0.608
	Female	1 (25.0%)	3 (75.0%)		
HIV Status	Negative	7 (53.8%)	6 (46.2%)	4.08 (0.99 - 16.87)	0.052
	Positive	6 (22.2%)	21 (77.8%)		
Syphilis Stage	Early Syphilis	7 (28.0%)	18 (72.0%)	0.58 (0.15 - 2.26)	0.329
	Late Latent	6 (40.0%)	9 (60.0%)		

Independent t-tests and Mann-Whitney U tests were conducted to compare continuous variables between the serological cure and serofast groups (Table 4). There were no statistically significant differences found in the mean duration of monitoring (p=0.793) or mean age (p=0.837). Furthermore, immunological markers, including absolute CD4 count

(417.9 vs. 448.9 cells/ μ L; $p=0.801$), CD4 percentage ($p=0.746$), CD8 percentage ($p=0.481$), and the CD4/CD8 ratio ($p=0.461$), did not differ significantly between the two groups.

Regarding serological markers, the baseline (pre-treatment) VDRL titers showed no significant difference between the two groups ($p=0.872$). However, a highly significant difference was observed in the post-treatment VDRL titers ($p < 0.001$). The serofast group had a significantly higher Mean Rank (26.59) for post-treatment titers compared to the serological cure group (Mean Rank 7.85), indicating that despite starting with similar baseline titers, the serofast group retained significantly higher antibody levels after treatment.

Table 4. Comparison of Clinical and Immunological Parameters by Outcome

Variable	Serological cure (Mean \pm SD)	Serofast (Mean \pm SD)	P-value	Test Method
Duration (months)	15.92 \pm 10.52	15.13 \pm 6.58	0.793	Indep. T-Test
Age (years)	29.23 \pm 7.34	28.63 \pm 9.12	0.837	Indep. T-Test
CD4 Count (cells/ μ L)	417.90 \pm 139.14	448.89 \pm 282.51	0.801	Indep. T-Test
CD4 Percentage (%)	15.91 \pm 6.91	17.21 \pm 8.75	0.746	Indep. T-Test
CD8 Percentage (%)	51.56 \pm 10.55	45.71 \pm 18.86	0.481	Indep. T-Test
CD4/CD8 Ratio	0.34 \pm 0.19	0.42 \pm 0.24	0.461	Indep. T-Test
CD8 Absolute	15.17 (Mean Rank)	11.61 (Mean Rank)	0.286	Mann-Whitney
VDRL Titer (Pre)	20.08 (Mean Rank)	20.70 (Mean Rank)	0.872	Mann-Whitney
VDRL Titer (Post)	7.85 (Mean Rank)	26.59 (Mean Rank)	< 0.001	Mann-Whitney

A Wilcoxon Signed Ranks Test (Table 5) was performed to evaluate the effectiveness of the treatment by comparing pre-injection and post-injection VDRL titers. The results demonstrated a statistically significant reduction in titers post-treatment ($Z = -5.090$, $p < 0.001$). Specifically, 34 subjects (85%) experienced a decrease in titer, while 6 subjects showed no change; no subjects experienced an increase in titer.

Table 5. Evaluation of Treatment Effectiveness (Pre- vs. Post-Treatment Titer)

Variable	N	Mean Rank	Sum of Ranks	Z Score	P-value
Post-Titer < Pre-Titer	34	17.50	595.00	-5.090	< 0.001
Post-Titer > Pre-Titer	0	.00	.00	-	-
Ties	6	-	-	-	-

Binary logistic regression was performed to determine independent predictors for the serofast outcome (Table 6). The model included HIV status, pre-treatment VDRL titer, and age. The model explained approximately 29.0% of the variance in the outcome (Nagelkerke $R^2 = 0.290$) and correctly classified 72.5% of cases.

The analysis revealed that HIV status was the only significant independent predictor of a Serofast outcome ($p=0.011$). Patients who were HIV positive had an Adjusted Odds Ratio (aOR) of 10.94 (95% CI: 1.72 - 69.65), indicating that HIV-positive patients were nearly 11 times more likely to experience a serofast state compared to HIV-negative patients, after

controlling for age and baseline VDRL titers. Neither pre-treatment VDRL titer ($p=0.058$) nor age ($p=0.200$) were significant predictors in the multivariate model.

Table 6. Multivariate Logistic Regression: Risk Factors for Serofast Outcome

Variable	B	S.E.	Sig. (p)	aOR (Exp B)	95% C.I. for aOR
HIV Status (Positive)	2.392	0.944	0.011	10.940	1.719 - 69.645
VDRL Titer (Pre)	-0.027	0.014	0.058	0.973	0.946 - 1.001
Age (Years)	-0.063	0.049	0.200	0.939	0.854 - 1.034
Constant	1.678	1.378	0.223	5.357	

DISCUSSION

The demographic analysis of the 40 subjects in this study revealed a predominance of young adults, with 50.0% aged 21–30 years, and a significant male majority (90.0%). This distribution aligns with global and national epidemiological trends reporting a resurgence of syphilis among men, particularly those in the sexually active reproductive age group (Achdiat *et al.*, 2025; WHO, 2020). The high proportion of males in this study is likely driven by the representation of men who have sex with men (MSM); notably, 60% of the total cohort identified as homosexual ($n=24$), and all subjects in this group were unmarried. This demographic profile is consistent with literature identifying MSM as a key population in the ongoing syphilis epidemic due to high-risk sexual networks (Tudor, 2024; Dela *et al.*, 2019).

Regarding the clinical stage, the study population showed a distribution across early latent (27.5%), late latent (37.5%), and secondary syphilis (35.0%). The substantial proportion of latent cases highlights the silent nature of the epidemic, where asymptomatic individuals may unknowingly transmit the infection or progress to tertiary complications if untreated. Bivariate analysis indicated that age, gender, marital status, and syphilis stage were not significantly associated with the treatment outcome (serofast vs. serological cure), suggesting that demographic factors alone are not the primary determinants of serological response in this cohort.

The most significant finding of this study was the strong association between HIV status and the serofast outcome. In the multivariate logistic regression analysis, HIV positivity was identified as the sole significant independent predictor ($p=0.011$). Patients with HIV co-infection were nearly 11 times more likely to experience a serofast state compared to HIV-negative patients (aOR = 10.94; 95% CI: 1.72 - 69.65).

This finding corroborates previous studies suggesting that HIV co-infection complicates syphilis serological responses (Fan *et al.*, 2021; Seña *et al.*, 2015). The mechanism is likely multifactorial. HIV induces chronic immune activation and B-cell dysfunction, which may lead to the persistent production of non-treponemal antibodies even after bacterial clearance (Kenyon *et al.*, 2017). Furthermore, the interaction between HIV and *T. pallidum* may impair the host's ability to fully clear treponemal antigens, maintaining a state of chronic immune stimulation that manifests as a serofast result (Cao *et al.*, 2024). The high prevalence of HIV in the serofast group (77.8%) compared to the serological cure group (46.2%) reinforces the need for vigilant monitoring of serological responses in HIV-positive patients.

Interestingly, despite the strong link between HIV and serofast status, this study found no statistically significant differences in quantitative immunological markers between the

serological cure and serofast groups. The mean absolute CD4 count (417.9 vs. 448.9 cells/ μ L; $p=0.801$), CD4 percentage ($p=0.746$), CD8 percentage ($p=0.481$), and CD4/CD8 ratio ($p=0.461$) were comparable between the two groups.

These results contrast with some literature suggesting that lower CD4 counts are predictive of serological failure. However, our findings align with other studies indicating that in the era of antiretroviral therapy (ART), absolute CD4 counts may not always correlate linearly with functional immune responses to syphilis (Seña *et al.*, 2015). It is possible that immune dysregulation in serofast patients involves functional defects in T-cell signaling or cytokine production such as elevated IL-6 or TNF- α levels rather than simple quantitative deficits in CD4 or CD8 populations (Okay *et al.*, 2020; Pastuszczak *et al.*, 2017). Additionally, since HIV status was a strong predictor while CD4 count was not, this suggests that HIV-related factors other than T-cell depletion such as chronic inflammation or specific B-cell dysregulation may drive the serofast phenotype.

The analysis of serological markers showed that baseline (pre-injection) VDRL titers were not significantly different between the serological cure and serofast groups ($p=0.872$). This refutes the hypothesis that higher baseline titers always lead to a faster serological decline in this specific cohort, a finding that varies across the literature (Czarny *et al.*, 2025; Seña *et al.*, 2015).

However, treatment effectiveness was evident across the total cohort, with a statistically significant reduction in titers post-treatment (Wilcoxon Signed Rank Test, $p<0.001$). The divergence in outcomes was driven by the magnitude of this decline. The serofast group had significantly higher post-treatment mean ranks compared to the serological cure group ($p<0.001$). This confirms that while serofast patients do respond to therapy (as evidenced by some titer reduction), they fail to achieve the magnitude of decline required for the definition of cure. This stalled response supports the definition of serofast as a distinct immunological state rather than a complete treatment failure or reinfection (Paul *et al.*, 2021).

CONCLUSION

This study demonstrates that HIV co-infection is a potent independent predictor of the Sero fast state in syphilis patients, elevating the risk approximately 11-fold, while quantitative cellular immune markers (CD4 and CD8 counts) showed no significant difference between outcome groups pointing to functional immune dysregulation, rather than simple T-cell depletion, as the likely driver of antibody persistence. These findings underscore the need for integrated, vigilant serological monitoring in HIV-syphilis co-infected individuals, for whom standard cure criteria may be more difficult to achieve despite adequate therapy. Future research should investigate the specific functional immune pathways involved, particularly the roles of B-cell dysregulation, chronic immune activation, and cytokine profiles such as IL-6 and TNF- α , in larger and more diverse cohorts, to develop targeted biomarkers and refined treatment monitoring protocols for this high-risk population.

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