Factors Associated with Serological Failure After Syphilis Therapy in People with HIV-1 with Undetectable Viral Load

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ABSTRACT

Introduction: Coinfection of human immunodeficiency virus and syphilis pose a global health challenge and present diagnostic complexities. People with human immunodeficiency virus experience a higher rate of syphilis serological failure than patients without human immunodeficiency virus.

Objective: To assess laboratory characteristics and the course of syphilis treatment in a group of Polish patients with human immunodeficiency virus-1.

Material and methods: Demographic and laboratory data of patients with human immunodeficiency virus-1 and syphilis admitted to one of the infectious diseases departments in Poland in the years 2008–2023 were collected retrospectively. The χ^2 or Fisher's exact tests were used to assess differences in categorical variables. Logistic regression analyses evaluated factors related to serological treatment failure in syphilis.

Results: There were $n = 59$ syphilis infections among $n = 43$ patients. All patients were male, aged from 21 to 60, all were taking antiretroviral treatment (ART) and had undetectable viral load. Among all syphilis infections, $n = 34$ were primary, $n = 3$ were late, and $n = 22$ were syphilis of unknown duration. The mean lymphocyte T CD4 count was 621 cells/µl. In $n = 11$ (18.64%) infections there was no 4-fold decline in VDRL in the course of 12 months after treatment. Univariate and multivariate analysis showed VDRL titer < 1 : 32 to be associated with higher odds of serological failure.

Conclusions: People with HIV regardless of their undetectable HIV-1 viral load and their lymphocyte T CD4 count are at risk of syphilis serological failure. Those with VDRL titer < 32 might be at higher risk of serological treatment failure. Regular screening for syphilis and monitoring of serological response to syphilis treatment is recommended for people with HIV-1.

Key words: human immunodeficiency virus, syphilis, serological failure.

INTRODUCTION

Syphilis is a common sexually transmitted disease (STD) resulting from *Treponema pallidum* bacterial infection. In 2020 worldwide there were 7.1 million new cases of syphilis [1]. The prevalence of syphilis infection in Poland reached a 77% rise with nearly 2000 new infections in the year 2022 in comparison to 2021. While

the absolute number of hospitalizations increased from 177 in 2021 to 258 in 2022, their proportion relative to the total number of reported syphilis cases declined, representing 15.7% in 2021 and 13% in 2022 [2].

Treponema pallidum can be transmitted through sexual contact, blood transfusion (rarely, as the blood of donors is screened for *T. pallidum*), or through the placenta [3]. The manifestation of symptoms is caused by the inflammatory response elicited by the bacteria and bacterial constituents such as specific lipoproteins [4]. The disease manifests with various symptoms depending on the stage of the infection [5]. Patients with primary syphilis usually present with a painless lesion at the site of inoculation (chancre). Secondary syphilis exhibits constitutional symptoms such as fever, headache, malaise, and sore throat. Some patients will also have enlarged lymph nodes and a diffuse, symmetric, macular, or papular rash covering the trunk and extremities. Untreated syphilis might lead to late syphilis stage with cardiovascular, ocular, neural, and gummatous syphilis [6]. Tests for syphilis can be categorized into treponemal and non-treponemal types. The Venereal Disease Research Laboratory (VDRL) test is one of the most commonly used non-treponemal tests. It is utilized for initial screening and for monitoring the response to treatment, as the antibody titre decreases with successful therapy [7]. This test is valued for its simplicity, low cost, and high sensitivity in the early stages of syphilis.

People with syphilis are more exposed to other STDs such as human immunodeficiency virus (HIV), chlamydia, or gonorrhea due to the syphilis ulcers that provide the portal of entry for other sexually transmitted pathogens [8, 9]. Men who have sex with men can be more at risk of acquiring syphilis due to an increase in unprotected, condomless sexual behaviors in recent years in this group of people [10]. Also, the coinfection with HIV-1 and syphilis raises a considerable global health problem and can be diagnostically challenging. HIV-1 can alter the symptoms of syphilis either by aggravating them or by suppressing them [11]. Moreover, people with HIV experience a higher rate of syphilis serological failure than patients without HIV [12]. For that, it is essential to regularly screen people with HIV for syphilis and to screen all patients with any STD for HIV.

OBJECTIVE

The objective of this study was to assess laboratory characteristics and the course of syphilis treatment in a group of Polish patients with HIV-1 who are taking antiretroviral treatment.

MATERIAL AND METHODS

Medical records of patients coinfected with HIV-1 and syphilis admitted to one of the infectious diseases departments in Poland from 2008 to 2023 with syphilis treatment using penicillin benzathine, penicillin procaine, doxycycline, or ceftriaxone were collected and analyzed. Demographic and laboratory data, such as age, gender, lymphocyte T CD4 count, class of antiretroviral treatment (ART), stage of syphilis, past syphilis infection, VDRL titer and type of syphilis treatment were analyzed.

The first day of therapy for syphilis also marked the beginning of laboratory testing. All tests were performed at least three times starting from the first day of syphilis therapy. The post-treatment data were collected from tests carried out during the visit scheduled at 12 months. Inclusion criteria for our study involved all syphilis infections in adult patients (≥ 18 years old) with confirmed HIV-1 with completed syphilis treatment. We excluded from the analysis syphilis infections in individuals who: were younger than 18, had detectable HIV-1 viral load, had a break between follow-up tests longer than a year, had shorter observation than 12 months or were pregnant.

Serological failure after treatment was defined as a lack of at least a 4-fold decline in VDRL titers compared to the pre-treatment values within 12 months. Syphilis diagnosis was based on clinical manifestations and supported by laboratory examination in agreement with the Guidelines of the Polish Dermatological Society, the International Union Against Sexually Transmitted Infections and the Center for Diseases Control STD Treatment Guidelines [5, 13, 14].

Statistical analysis

The χ^2 or Fisher's exact tests were performed to evaluate the difference for categorical variables. Univariate and multivariable logistic regression analysis was used to evaluate the factors associated with serological treatment failure of syphilis. The *p*-value was set at 0.05. All statistical analyses were performed using R statistical software version 4.4.1.

RESULTS

There were $n = 59$ syphilis infections among $n = 43$ patients. All patients who met the inclusion criteria for this study were men having sex with men. The patients' ages ranged from 21 to 60 years (mean: 37.6, standard deviation: 8.1). During the 12 months' follow-up there were 27 reinfections of syphilis. Among all syphilis infections, $n = 34$ were primary, $n = 3$ were late, and $n = 22$ were syphilis of unknown duration. The mean lymphocyte T CD4 count was 621 cells/ml and did not differ significantly between patients who responded to syphilis treatment and who did not. Three of those who had treatment failure had a number of lymphocyte T CD4 count < 500 cells/ml. All patients in this study were receiving antiretroviral treatment and had an undetectable viral load. $N = 18$ patients had chronic diseases

Table 1. Baseline characteristics of analyzed syphilis infections according to the decrease in VDRL titer. Results are shown as counts and percentages for categorical variables, and as means and standard deviations for quantitative variables

Parameter	All infections (n = 59)	Infections with a significant decrease in VDRL titer after treatment (n = 48)	Infections with no significant decrease in VDRL titer after treatment (n = 11)	P-value
Age [years]	37.6 ±8.1	38.1 ±8.6	35.2 ±5.1	0.286
Syphilis stage, *n* (%)				
Early	34 (57.63)	29 (60.42)	5 (45.45)	0.439
Late	3 (5.08)	2 (4.17)	1 (9.09)	
Unknown duration	22 (37.29)	17 (35.42)	5 (45.45)	
Syphilis treatment, *n* (%)				
Penicillin	42 (71.19)	31 (64.58)	10 (91.0)	0.146
Doxycycline	28 (47.46)	23 (47.92)	5 (45.45)	0.883
Ceftriaxone	9 (15.25)	8 (16.67)	1 (9.09)	1.000
Baseline VDRL titer, *n* (%)				
≥ 1 : 32	41 (69.49)	38 (79.17)	3 (27.27)	0.002
< 1 : 32	18 (30.51)	10 (20.83)	8 (72.73)	
Syphilis episode				
First episode, *n* (%)	32 (54.24)	28 (58.33)	4 (36.36)	0.187
Reinfection during 12 months' follow-up, *n* (%)	27 (45.76)	20 (41.67)	7 (63.64)	
CD4 cell count [cells/ml]	621 ±285	604 ±279	690 ±315	0.374
CD4:CD8	0.75 ±0.37	0.73 ±0.36	0.86 ±0.40	0.279
ART, *n* (%)				
InSTI	38 (64.41)	31 (64.58)	9 (81.82)	1.000
NRTI	55 (93.22)	46 (95.83)	9 (81.82)	0.154
PI	19 (32.20)	15 (31.25)	4 (36.36)	0.734
NNRTI	8 (13.56)	7 (14.58)	1 (9.09)	1.000

InSTI – integrase inhibitors, NRTI – nucleoside reverse transcriptase inhibitors, PI – protease inhibitors, NNRTI – non-nucleoside reverse transcriptase inhibitors.

(n = 11 chronic liver diseases, n = 6 autoimmune diseases, n = 2 hypertension and n = valve insufficiency, n = 1 non-Hodgkin lymphoma). Characteristics of the examined syphilis infections are shown in Table 1.

In n = 11 (18.64%) episodes of syphilis the expected 4-fold VDRL titer decline was not reached within the 12 months' follow-up. Of those, five were primary stage infections, one was late and five were of unknown duration. We analyzed factors associated with serological failure in Table 2. Univariate and multivariate analysis showed baseline VDRL < 1 : 32 to be associated with higher odds of serological failure of syphilis treatment. Neither age, syphilis stage, syphilis treatment, syphilis episode, nor CD4:CD8 ratio were associated with serological failure.

DISCUSSION

The European AIDS Clinical Society (EACS) and the Polish AIDS Society (PTN AIDS) recommend annual screening for syphilis of all people with HIV, and more frequent screening if symptomatic or with a history of unprotected sexual contact [15]. There has been a rising incidence of syphilis, particularly among men who have sex with men [16]. Multiple infections have also been observed in some patients, supporting the need for intensified prevention strategies [17]. Early detection of syphilis facilitates the prevention of further transmissions and better treatment outcomes.

In this analysis, 11 (18.64%) patients had serological failure to syphilis therapy. Other studies have shown a lack of treatment response in 9 to 17% of studied patients with HIV [18, 19]. The majority of patients with treatment failure in our study (n = 8, 73%) had a lymphocyte T CD4 count above 500 cells/ml and lymphocyte T CD4 count was not correlated with syphilis treatment failure. Some studies have shown contradictory results regarding the correlation of lymphocyte T CD4 count and syphilis serological treatment failure. In a study by Ghanem *et al.*, lymphocyte T CD4 count below 200 cells/ml was asso-

Table 2. Risk factors associated with serological failure measured on the first day of syphilis treatment – univariate and multivariate analysis

Parameter	OR (95% CI)	*P*-value	aOR (95% CI)	*P*-value
Age [years]				
< 35		Ref.		
≥ 35	1.27 (0.265–5.80)	0.745	6.25 (0.70–109)	0.140
Syphilis stage				
Early		Ref.		
Late	2.79 (0.041–62.5)	0.421	4.99 (0.06–368)	0.456
Unknown duration	1.69 (0.336–8.55)	0.491	12.0 (1.07–379)	0.080
Syphilis treatment				
Penicillin		Ref.		
No penicillin	0.186 (0.003–1.51)	0.146	0.187 (0.006–2.15)	0.228
Baseline VDRL titer				
≥ 1 : 32		Ref.		
< 1 : 32	9.62 (1.89–66.7)	0.002	30.5 (3.41–547)	0.007
Syphilis episode				
First infection		Ref.		
Reinfection	2.41 (0.528–12.8)	0.314	2.53 (0.230–40.3)	0.463
CD4:CD8 ratio				
≥ 1		Ref.		
< 1	3.06 (0.613–15.2)	0.126	0.566 (0.04–7.02)	0.649

OR – odds ratio, aOR – adjusted odds ratio, Ref – refernce value.

ciated with a higher incidence of treatment failure, whereas in the study by Jinno *et al.*, a lymphocyte T CD4 value of above 350 cells/ml was associated with serological failure [18, 20]. The discrepancies between results in other studies and our results might need further investigation.

Based on the analyzed data, the stage of syphilis infection was not correlated with serological treatment failure of syphilis. The same number of patients did not reach the significant decrease in the VDRL titer both in the early stage syphilis and in the syphilis of unknown duration. According to some other studies, early syphilis is typically associated with a faster time to serological cure [21, 22]. In our study, only 3 patients presented with late-stage syphilis, limiting our ability to draw meaningful conclusions for this subgroup. However, according to Spagnuolo *et al.*, late syphilis was associated with a higher likelihood of serological failure in both univariate and multivariate analyses [23]. The VDRL titer < 1 : 32 was the only factor associated with a higher risk of treatment failure compared to a VDRL titer of ≥ 1 : 32. We found no comparable studies on the subject.

Cases of patients exhibiting serological failure after syphilis treatment have been extensively discussed in recent years; however, no definitive risk factors have been identified. It is postulated that the enduring presence of nontreponemal antibodies contributing to serological failure is correlated with compromised immune tolerance resulting in a slow response to the treatment with the eventual response later in time [24, 25]. In the study of Carlson *et al.*, it is suggested that the prolonged elimination of syphilis spirochetes may be associated with impaired activation of macrophages by CD4 T lymphocyte cells [26].

Based on the data presented in this study, the class of ART did not influence the immunological response to syphilis treatment. Limited research has examined the relationship between ART classes and syphilis outcome, but it has been confirmed that individuals receiving ART are less prone to experiencing serological failure after syphilis treatment compared to those without ART [20].

The study faced several limitations. The research was carried out at a single center and involved a small number of patients. Women did not participate in the study. No comparison with patients with HIV who had detectable viral load or a group of patients without HIV was carried out. None of the patients included in this study had symptoms of neurosyphilis and none had a lumbar puncture. A 12-month follow-up may be too short for a full evaluation of the effectiveness of treatment of late syphilis. While writing this study both the Centre for Disease Control and the Polish AIDS Society changed the recommendations and currently suggest that the time to the 4-fold decrease of VDRL in people with HIV might be until 24 months [27, 28]. In cases of se-

rological failure, further evaluation should include a detailed history focusing on potential incidental sexual contacts during follow-up, as well as additional diagnostic testing, particularly cerebrospinal fluid examination.

CONCLUSIONS

In this study, only the VDRL titer < 1 : 32 was correlated with the serological syphilis treatment failure. Undetectable HIV-1 VL and lymphocyte T CD4 count above 500 cells/ml does not guarantee treatment response to syphilis treatment. Monitoring the serological response to syphilis treatment is advised for all people with HIV-1, irrespective of ART efficacy or immune status. A longer than 12 months' follow-up after syphilis treatment might be needed in the group of patients with HIV. Cerebrospinal fluid examination should be considered for those who have serological failure after treatment of syphilis.

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ETHICAL APPROVAL

Approval (no. AKBE/96/2024) from the appropriate bioethics committee was obtained for the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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