Evaluation of syphilis co-infection and monitoring of rapid plasma reagin (RRP) titer according to syphilis-stage in human immunodeficiency virus-infected patients

İnsan immün yetmezlik virüsü ile enfekte hastalarda sifiliz ko-enfeksiyonunun değerlendirilmesi ve rapid plasma reagin (RRP) titresinin sifiliz evresine göre takibi

Abstract

Aim: Syphilis co-infection in Human Immunodeficiency Virus (HIV)-infected patients is associated with a delayed serological response. The aim of this study is to obtain current data on the frequency of HIV/syphilis co-infection, the monitoring of rapid plasma reagin (RPR) titer after treatment, and factors affecting the serologic response.

Methods: Serological tests for syphilis of HIV patients followed between January 2015 and March 2023 were evaluated retrospectively. Demographic data (age, sex), level of HIV ribonucleic acid (RNA), RPR, Treponema pallidum haemagglutination test (TPHA), and syphilis stage were obtained from the hospital electronic database. The serological response was defined according to Centers for Disease Control and Prevention (CDC) criteria.

Results: Syphilis co-infection was detected in 36.2% of the patients, all of the co-infected patients were male. Distribution of syphilis stage was primary 2.9%, secondary 9.7%, latent syphilis 44.6%, neurosyphilis 5.8%, and past syphilis 37% respectively. All patients with primary, secondary, and neurosyphilis had ≥4-fold decrease in RPR titer within 12 months after treatment, while two patients with latent syphilis didn't have a decrease in titer within 12-24 months. Overall serologic response was 95.8%. Comparing the time to a 4-fold decrease in the RPR titer in terms of syphilis stage, there was no statistically significant difference (p=0.878). Patients with initial RPR titer >1: 32 achieved faster serologic response than those with initial RPR titer ≤1: 32.

Conclusion: HIV/syphilis coinfection rate was notably high in our study. It is promising that most patients had a serologic response within the time frame defined by the CDC. However, It should be considered that treatment response may take longer in patients with an initial RPR titer≤32. Further prospective studies are needed to understand the factors associated with serologic outcomes in HIV/syphilis co-infected patients.

Keywords: Coinfection; human immunodeficiency virus; rapid plasma reagin; serologic response; syphilis

Öz

Amaç: İnsan Bağışıklık Yetmezliği Virüsü (Human Immunodeficiency Virus: HIV) hastalarındaki sifiliz koenfeksiyonu gecikmiş serolojik yanıt ile ilişkilidir. Bu çalışmanın amacı, HIV/sifiliz koenfeksiyonunun sıklığı, tedavi sonrası rapid plasma reagin (RPR) titresinin izlenmesi ve serolojik yanıtı etkileyen faktörler hakkında güncel veriler elde etmektir.

Yöntemler: Ocak 2015-Mart 2023 tarihleri arasında takip edilmiş HIV hastalarının sifiliz enfeksiyonuna yönelik serolojik testleri retrospektif olarak değerlendirildi. Demografik veriler (yaş, cinsiyet), HIV RNA seviyesi, RPR, Treponema pallidum hemaglütinasyon testi (TPHA) ve sifiliz evresi hastane elektronik veri tabanından elde edildi. Serolojik yanıt, Hastalık Kontrol ve Önleme Merkezi (CDC) kriterlerine göre tanımlandı.

Bulgular: Hastaların %36,2'sinde sifiliz koenfeksiyonu olduğu ve koenfekte hastaların tamamının erkek olduğu saptanmıştır. Sifiliz evresine göre dağılım sırasıyla, primer %2,9, sekonder %9,7, latent sifiliz %44,6, nörosifiliz %5,8 ve geçirilmiş sifiliz %37 şeklinde bulunmuştur. Primer, sekonder ve nörosifilizi olan tüm hastalarda tedaviden sonraki 12 ay içinde RPR titresinde ≥4 kat azalma olurken, latent sifilizli iki hastada 12-24 ay içinde titrede azalma olmamıştır. Buna göre genel serolojik yanıt %95.8 bulunmuştur. RPR titresindeki 4 kat azalmanın elde edildiği süre, sifiliz evreleri açısından karşılaştırıldığında, istatistiksel olarak anlamlı bir fark tespit edilmemiştir (p=0.878). Başlangıç RPR titresi >1:32 olan hastalar, başlangıç RPR titresi ≤1:32 olanlara göre daha hızlı serolojik yanıt elde etmiştir.

Sonuç: Çalışmamızda, HIV/sifiliz koenfeksiyon oranının oldukça yüksek olduğu gözlemlenmiştir. Hastaların çoğunda CDC'nin tanımladığı zaman aralığında serolojik yanıt alınması umut verici bulunmuştur. Ancak başlangıç RPR titresi 1≤32 olan hastalarda tedavi yanıtının daha uzun sürebileceği göz önünde bulundurulmalıdır. Bunun yanısıra, HIV/sifiliz koenfekte hastalarda serolojik yanıtla ilişkili faktörleri araştıran daha ileri prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: İnsan immün yetmezlik virüsü; koenfeksiyon; rapid plasma reagin; serolojik yanıt; sifiliz

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INTRODUCTION

Syphilis is a systemic infectious disease caused by *Treponema pallidum*. Since the transmission ways of human immunodeficiency virus (HIV) infection and syphilis are common, syphilis co-infection is frequently seen in HIV-infected individuals (1,2). It has been reported that there is a prominent increase in the number of new cases diagnosed with HIV in our country (3-6). In parallel with this, the prevalence of syphilis is gradually rising in HIV-infected patients (7-10). In addition, recent studies have shown that the rate of recurrent infection has reached alarming levels in HIV-infected male patients with a history of syphilis (2,11,12). While HIV/syphilis co-infection scales up the risk of HIV transmission due to the presence of syphilis-related genital/oral lesions, it can also affect the clinical course of syphilis by suppressing the host immune system (9,13). Previous studies described that HIV infection is associated with a higher rate of asymptomatic primary syphilis or more invasive disease manifestations in early syphilis (12,14). Therefore, monitoring of HIV-positive patients for syphilis is vital both to raise awareness of the increasing HIV/syphilis co-infection and to develop new intervention strategies.

Serology is the main tool in the diagnosis and treatment monitoring of syphilis. The reverse algorithm approach is more effective for the screening of syphilis in HIV-infected populations, particularly for early and latent syphilis (12). Some studies have reported that treatment response to syphilis infection in HIV patients is lower and delayed than in HIV-negative patients. (15,16). Initial rapid plasma reagent (RPR) titer and syphilis stage have been found to be associated with the duration of serologic response in HIV/syphilis co-infection. But, data regarding serological response and treatment failure in HIV-infected patients with syphilis are discordant (15-18).

Although there are many studies on the rate and risk factors of HIV/syphilis co-infection in our country (19-21), few data are available on post-treatment RPR follow-up and serological response in HIV-positive patients infected with syphilis (3,10). Therefore, in this study, we aimed to monitor the rate of syphilis co-infection, RPR titer after treatment, time to serologic response, and to establish the factors associated with serologic outcome in HIV-infected patients.

MATERIAL AND METHODS

Study design and patients

This retrospective study was conducted using data from confirmed HIV patients admitted to Haydarpaşa Numune Training and Research Hospital between 1 January 2015 and 1 March 2023. The demographic data (age, sex), level of HIV RNA, syphilis serology including RPR, Treponema pallidum haemagglutination test (TPHA), Venereal Disease Research Laboratory (VDRL) test in cerebrospinal fluid (CSF), and syphilis stage were obtained from electronic medical records. Patients with incomplete or unclear data were excluded from the study.

Serological tests

The reverse algorithm was used in the diagnosis of syphilis (21). The specific IgG+ IgM antibodies to *Treponema pallidum* were performed as the first diagnostic test based on chemiluminescent method with a Syphilis TP kit in ARCHITECT i2000SR (Abbott, Germany) device. According to the manufacturer's instructions, those with a sample/cut-off (S/ CO) value of ≥1 were defined as reactive. Secondly, RPR (Omega, UK) test and TPHA (Plasmatec, England) test were carried out in all patients with reactive specific antibodies. For the diagnosis of neurosyphilis, VDRL (Omega, UK), and when needed fluorescent treponemal-antibody absorption tests (FTA-ABS) (Euroimmun, Germany) in CSF were tested, in line with CDC recommendations (22). Serum RPR and TPHA titers at the time of HIV diagnosis, pre and post-treatment RPR titer of the patients treated for syphilis, and time to ≥4-fold reduction in RPR titer after treatment were recorded.

Definitions

The syphilis stage (primary, secondary, latent, neurosyphilis, and past syphilis) was determined in accordance with CDC sexually transmitted diseases treatment guidelines (22). Primary syphilis was diagnosed in the presence of chancre or chancres; secondary syphilis was diagnosed in the presence of characteristic skin rash and mucocutaneous lesions; latent syphilis was considered in patients with positive nontreponemal and treponemal tests without any clinical signs and symptoms. Neurosyphilis was diagnosed on

a combination of CSF tests (CSF cell count, reactive CSF-VDRL, and/or FTA-ABS) in the presence of reactive serologic test results and neurologic signs and symptoms (22). RPR negative/TPHA positive patients who had previously been treated for syphilis were considered as past syphilis infection.

Serological response after treatment is defined according to the CDC (22). An adequate serologic response was considered as ≥4-fold decrease in RPR titer by 6–12 months for primary and secondary syphilis, and by 12–24 months for latent syphilis and neurosyphilis. Since patients with initial RPR titers with the values of 1:1 or 1:2 had no follow-up RPR titer, they were excluded from all analyses of serological responses.

HIV viral load

HIV RNA levels were assessed using the RT-PCR method (ARTUS QIAGEN HI Virus-1RG, Germany), according to the manufacturer's instructions.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences version 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were computed as mean, standard deviation (SD), count, and percent frequencies according to the types of the variables. One-way ANOVA and Kruskal-Wallis test were used to compare the groups in terms of the data obtained. Correlations between measurements were evaluated by Spearman rank correlation analysis. A p-value of <0.05 was accepted as statistically significant.

This study was approved by Clinical Research Ethics Committee of Haydarpaşa Numune Training and Research Hospital (date: 08.05.2023, decision no: KK86).

RESULTS

During the study period, a total of 284 HIV infected patients were followed, of whom 268 (94.3%) were male and the mean age was 39.4 (21-77). Syphilis co-infection was detected in 36.2% of the patients (n=103), and all of them were male (100%), with a mean age of 40 (25-77). It was determined that the mean age was not significantly different according to the syphilis stage (p=0.336). Distribution of the patients by syphilis stage was primary 2.9%, secondary 9.7%, latent syphilis 44.6%, neurosyphilis 5.8%, and past syphilis 37%, respectively. HIV-RNA was found to be negative in 56.1% of all patients. Although the rate of HIV-RNA negativity was lower in the neurosyphilis stage than the others (16.7%), the differences between them were not statistically significant (p=0.336, Pearson chi-square test). Demographic, clinical, and serological data of the patients are presented in **Table 1**.

Among a total of 103 patients, there were 46 patients diagnosed with latent syphilis. Of these, 17 patients with no data on RPR follow-up or treatment and an additional 38 patients with past syphilis who had been previously treated for syphilis were excluded from serologic response analyses. A total of 48 patients (3 primary, 10 secondary, 29 latent, 6 neurosyphilis) were treated for syphilis and followed up with RPR. Among these patients, all patients with primary, secondary, and neurosyphilis had ≥4-fold decrease in RPR titer within 12 months, while two patients with latent syphilis did not have a decrease in titer within 12-24 months **(Table 2)**. Overall serologic response was 95.8% regardless of the stage.

Among 46 patients with treatment response, the mean time to a ≥4-fold decrease was found to be 6, 4.7, 6.3, and 4.6 months for primary, secondary, latent, and neurosyphilis, respectively. When the time to a 4-fold decrease in the RPR titer was compared in terms of syphilis stages, there was no statistically significant difference (p=0.878, Kruskal-Wallis test) **(Table 3)**.

The degree of the relationship between the initial RPR titer and the time to a 4-fold decrease was found to be statistically significant (p=0.043, Spearman rank correlation analysis). According to this result, it was considered that as the initial RPR titer increases, the time for a 4-fold decrease becomes shorter. The mean time to ≥4-fold decrease in RPR titer was 6.84 months in patients with initial RPR titer ≤32, and 4.5 months in patients with >1:32 titer. These results indicate that the titer decrease takes longer in those with an initial titer of ≤32 (p=0.049, Kruskal-Wallis test) **(Table 4)**.

DISCUSSION

Syphilis co-infection in HIV-infected individuals shows a notable upward trend worldwide (1). Recent studies in Italy, France, Malaysia, Chad, Thai-

Table 1. Demographic, clinical and serological data of the patients with HIV/syphilis co-infection.

Stage	Number of patients n (%)	Age (year) mean (range)	HIV RNA (copies/mL) mean (range)	HIV RNA Negativity* (%)	Initial RPR titer mean (range)	Initial TPHA titer mean (range)
Primary	3 (2.9%)	31 (29-34)	61 (0- 185)	66.7%	1:64 (1:32- 1:128)	1:1280 (1:1280-:2560)
Secondary	10 (9.7%)	37 (25-62)	569883 (0- 4400824)	50%	1:64 (1:8- 1:256)	1:2560 (1:320-1:2560)
Latent syphilis	46 (44.6%)	40 (26-77)	436199 (0- 20768625)	51.8%	1:8 (neg- 1:32)	1:1280 (1:80-1:2560)
Neurosyphilis	6 (5.8%)	43 (26-58)	253365 (0- 918497)	16.7%	1:256 (1:64-1:512)	1:2560 (1:2560-1:2560)
Past syphilis	38 (37%)	40 (28-48)	786112 (0-802770)	66%	neg	1:1280 (1:80-1:2560)

*Pearson chi-square test (p=0.336) RPR: rapid plasma reagin TPHA: Treponema pallidum hemagglutination assay HIV RNA: human immunodeficiency virus ribonucleic acid.

Table 2. Percentage for achieving a 4-fold decrease according to stage (n:48)

	Stage	Total, n	Yes, n (%)	No, n (%)
Achieving a 4-fold decrease				
	Primary syphilis	3	3 (100)	0 (0)
	Secondary syphilis	10	10 (100)	0 (0)
	Latent syphilis	29	27 (93.4)	2 (6.6)
	Neurosyphilis*	6	6 (100)	0 (0)

* Rapid plasma reagin (RPR) test in serum and VDRL test (Venereal Disease Research Laboratory) in cerebrospinal fluid were performed.

Table 3. Comparison of initial RPR titer, treatment response, and the time to a 4-fold decrease according to syphilis stages in patients with serological response (n:46)

	Stages	n	Mean	SD
Time to a 4-fold* decrease (month)	primary	3	6.3	3.786
	secondary	10	4.7	2.438
	latent	27£	6.2	4.362
	neurosyphilis#	6	4.6	1.033

RPR; rapid plasma reagin (serum) *Kruskal-Wallis test (p=0.878) £27 of 29 patients had a serologic response.
#RPR test in serum and VDRL test (Venereal Disease Research Laboratory) in cerebrospinal fluid were performed.
SD: standard deviation.

Table 4. The mean time for a 4-fold decrease compared to the initial RPR titer (n:46)

Initial RPR Titer*	n	Mean (month)	SD	Percentiles		
				25th	Median	75th
≤32	25	6.84	4.130	3.00	7.00	10.00
>32	21	4.52	2.732	3.00	4.00	5.00

*Kruskal-Wallis test, Spearman rank correlation analysis (p=0.043)
RPR: Rapid plasma, SD: Standard deviation

land, USA, and Mexico found a high prevalence of HIV/syphilis co-infection ranging from 14 - 25% (2,11,14,17,18,23,24). When studies conducted in our country were analyzed, it was observed that the HIV/syphilis co-infection rate increased from 8% to 30.2% over the years (8,10,21). In these studies, it has been reported that the number of newly diagnosed HIV-positive patients is increasing every year and in parallel with this, the seroprevalence of syphilis is also rising. Similarly, the high rate we found in our study (36.2%) indicates that the increase of syphilis in HIV-infected patients continues.

Risk factors associated with HIV/syphilis co-infection include male sex, being male who has sex with a male (MSM), and controlled HIV infection on antiretroviral therapy (undetectable HIV RNA) (1,2,11,15). The high prevalence of syphilis in MSM is linked with high-risk sexual behaviors and poor condom usage in this population (1,15,19). The CDC reported in 2021 that the prevalence of syphilis is increasing among HIV-infected homosexual and bisexual men (25). In addition, data from various studies conducted both in Turkiye and other countries indicate that the rate of male patients with HIV/syphilis co-infection was found to be between 92.4% and 100% (15,16,19,20). Korkusuz et al. (19) and Öztürk et al. (3) found in their study that the seroprevalence of syphilis in MSM was statistically higher than that of heterosexual men. In a mathematical modeling study conducted by Sayan et al. (5) in 2017, it was stated that the epidemic size of HIV-infected MSM individuals in Istanbul (our study region) was higher than in other cities, and therefore, an extreme increase in HIV/syphilis co-infection especially in Istanbul, can be expected in the near future. Although we do not have precise data on the sexual behavior of the patients due to the retrospective data collection, the fact that all of the patients with HIV/syphilis co-infection were male and the high prevalence of 36.2% that we found five years after their study reveals the accuracy of the prediction of Sayan et al.

It was reported that providing long-term virologic suppression with anti-retroviral therapy creates a false perception of trust in patients; and increases the rate of unprotected sexual intercourse, which leads to an increase in sexually transmitted infections including syphilis (11,16). In the studies by Lemmet et al. (11) and Lin et al. (16), it was found that 88.7% and 91.8% of syphilis co-infected patients had negative HIV-RNA levels, respectively, and the frequency of syphilis co-infection was statistically higher in patients with negative or undetectable HIV viral load. In our study, although there was no statistically significant difference according to syphilis stage, it was noteworthy that 56.1% of patients co-infected with syphilis had negative HIV-RNA levels. This result may be an indication that syphilis is encountered due to a lack of attention to sexual protection methods due to the thought that the risk of HIV transmission has been reduced, in line with the above-mentioned literature.

Some studies have reported that treatment response to syphilis infection in HIV patients is lower than in HIV-negative patients and that a 4-fold decrease in RPR titer takes longer (15,16). Lin et al. (16) found that serologic responses of primary and secondary syphilis with a rate of 73.4% at 12 months were significantly poorer. On the other hand, there are also studies in which appropriate serologic responses were obtained in HIV-positive patients within the time period determined according to CDC criteria (max. 12 months for primary and secondary syphilis, max. 24 months for latent syphilis and neurosyphilis) (2,26,27). For example, in a recent study by Ren et al. (26), a serologic response was observed in 94% of patients with primary and secondary syphilis, 90.3% of patients with latent syphilis, and 96.7% of patients with neurosyphilis. Similarly, Marchese et al. (2) reported that the majority of HIV-positive patients (90%) infected with syphilis obtained an adequate serologic response. In a study by Öztürk (3), in which no stage classification was made, the rate of achieving a 4-fold reduction after 3/6 months after treatment was found to be 82% in general. In our study, only two of the patients who were followed up after syphilis treatment did not have a 4-fold decrease in RPR titer and the overall treatment response was 95.8% regardless of the stage. We think that achieving a titer decline within an average of six months can be an important prognostic indicator for the clinician. When analyzed according to the stages, it was found that serologic response was achieved in all patients with primary, secondary, and neurosyphilis (100%),

while this rate was 93.4% in patients with latent syphilis infection. Our results are compatible with studies showing a high rate of treatment failure in patients with latent syphilis (15,27).

In HIV-infected patients, the time to a 4-fold decline in RPR titer after treatment may differ in terms of syphilis stage (2,5,18). However, in our study, unlike the literature, we found that the duration of serological response did not show a statistically significant difference between syphilis stages. However, it should be noted that diversity in the categorization of syphilis stages and RPR follow-up frequencies in previous studies make it difficult to compare the data. Therefore, more comprehensive and multicenter studies are needed both for the confirmation of our results and for a clearer understanding of this issue in HIV-infected patients in our region.

The initial RPR titer, one of the predictors of serologic response, in HIV patients infected with syphilis was examined in previous studies, and controversial results were found. Ren et al. (26) found that patients with higher pre-treatment titers were less likely to reach a negative RPR. However, Marchese et al. (2) observed that the time to obtain a serological response was longer in patients with a lower initial RPR titer. Similarly, Lin et al. (16) stated that RPR titer was positively associated with serologic response. The researchers noted that higher RPR titers may be caused by a stronger immunological response, which is associated with a more effective eradication of *T. pallidum*. We also observed that as the initial RPR titer increases, the time for a 4-fold decrease becomes shorter, and patients with first RPR titer >1:32 achieved faster serologic response than those with first RPR titer ≤1:32, which was compatible with results by Spagnu et al. (15).

The impact of HIV viral load on the serologic response to syphilis is uncertain (2,15). In our study, viral load was not associated with serologic response as reported in some previous studies (2,16,26).

Our study has several limitations. First, the study was retrospectively designed and important data such as patients' sexual risk behavior, the rate of reinfection with syphilis, and serofast status could not be obtained. Secondly, the frequency and duration of serological follow-up of some patients included in the study were different according to clinicians. In addition, since it was a single-center study, our results do not reflect all the data of the region.

Our results showed that the rate of syphilis co-infection continues to increase remarkably in HIV-infected patients in Istanbul, and therefore patients should be effectively informed about safe sexual intercourse. Furthermore, a ≥4-fold reduction in RPR within the CDC-defined time frame in 95.8% of patients after treatment is promising. It should be considered that treatment response may take longer in patients with an initial RPR titer ≤32, regardless of the stage. Determination of syphilis serology at the time of diagnosis in all HIV-infected patients and subsequent RPR follow-up, especially in people with risky sexual behavior, is critical for early diagnosis and treatment. This study provides valuable data regarding the predictors associated with serologic response in HIV/syphilis co-infected patients, which will be helpful for clinicians in managing this co-infection. However, it is essential that further prospective studies be undertaken to understand which other factors are related to this topic.

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Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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