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Research Article

Seroprevalence and Risk Factors of Syphilis Coinfection in People Living with HIV

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Abstract

Objectives: This study aimed to determine syphilis coinfection prevalence in people living with HIV (PLHIV) and risk factors for coinfection.

Methods: This single-center retrospective cohort study screened PLHIV who were monitored in our center between March 2000 and February 2020 via the hospital's database and analyzed them by grouping as TPHA-positive and TPHA-negative. TPHA positivity was considered as indicative of *Treponema pallidum* exposure.

Results: The study included 474 PLHIV of whom median age (IQR) was 37 (30-47), and 429 (90.5%) were male. Of the male participants, 206 (47.9%) were MSM. The syphilis coinfection rate was 30.2% (143/474). Among the participants with syphilis coinfection, 80 (16.9%) were found to be coinfected with syphilis at the time of their HIV diagnosis, while 63 (13.3%) got infected with syphilis at a median (IQR) time of 60 (36-84) months into their HIV follow-up and treatment. Syphilis coinfection was related to being male (p<0.001), MSM (p=0.008) and single (p=0.007). Regular condom use was inversely related to syphilis coinfection (p=0.002).

Conclusion: HIV and syphilis have similar transmission routes, and HIV and syphilis coinfection is common among men, MSM and people who do not use condoms. PLHIV should be tested regularly for syphilis and informed about risky sexual behaviors and protection methods.

Keywords: Coinfection, human immunodeficiency virus, syphilis

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Syphilis, which is caused by *Treponema pallidum*, was discovered in the 15th century and has caused numerous mortalities and morbidities for more than 500 years. These effects of the disease diminished with the discovery of penicillin in the 1940s.[1] The incidence of syphilis increased again after the 1990s with human immunodeficiency virus (HIV) infection, and outbreaks were seen in North America, Europe and Australia in the early 2000s.[2,3] Because both HIV and syphilis are sexually transmitted diseases, their coinfection is not surprising. Men who have sex with men (MSM), sex workers, drug addicts and those with multiple partners are in the risk group.[4] Studies have reported the prevalence of syphilis coinfection among people living with HIV (PLHIV) between 6.21% and 46.5% worldwide.[5-11]

Syphilis increases the risk of the transmission of HIV infection. This condition occurs when oral, genital and anal ulcers are bleeding easily during sexual contact. Syphilis

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changes the course of HIV infection and causes progression by affecting the humoral and cellular immune systems. HIV infection may also change the typical course of syphilis infection.[4,12,13]

Preventive programs related to HIV and the common use of antiretroviral therapy have transformed HIV infection cases from fatal diseases to chronic diseases.[14,15] Thus, patients' quality of life increases, their lifespan is prolonged, and the risk of sexual transmission of their infection decreases. This condition causes the continuation of unprotected and risky sexual behaviors and increases the rates of other sexually transmitted diseases.[15]

Being aware of different syphilis presentations in patients infected with HIV, preventing new syphilis infections, and early diagnosis and treatment are significant in reducing the spread of both diseases. The Centers for Disease Control and Prevention (CDC) recommends screening for syphilis in sexually active individuals with HIV at their initial HIV examination and at least once a year thereafter.[16] This study aimed to determine the prevalence of syphilis coinfection in PLHIV who were followed in the clinic and risk factors of coinfection and to review protective and preventive measures.

Methods

This single-center retrospective cohort study was conducted in Medeniyet University Goztepe Training and Research Hospital. The ethics committee approval of the study was obtained from the Medeniyet University Goztepe Training and Research Hospital Ethics Committee with the date of 19.02.2020 and number of 2020/0122.

In this study, PLHIV who were monitored between March 2000 and February 2020 were retrospectively screened on the hospital's database and were determined. The patients' age, sex, education level, marital status, ways of HIV transmission, condom use status, disease follow-up duration, HIV RNA during diagnosis, CD4 T lymphocyte counts, RPR (rapid plasma reagin) and TPHA (*Treponema pallidum* hemagglutination assay) results were recorded on a form. HIV tests were performed using the enzyme-linked immunosorbent assay (ELISA) method, while HIV RNA levels were measured with the polymerase chain reaction (PCR) method (ARTUS QIAGEN HI Virus-1RG RT-PCR). CD4 T lymphocyte numbers were calculated by standard flow cytometry (FACSCalibur, Becton Dickinson). Serum RPR values were measured with the chemiluminescence method (ARCHITECT Syphilis kit), and TPHA was measured with a manual kit (PLASMATECT TPHA kit).

Serum RPR and TPHA tests were used for screening at the time of HIV diagnosis and at annual follow-up. TPHA positivity (with positive or negative RPR) was accepted as an indicator of exposure to *T. Pallidum*.

The patients with neurological symptoms and those with CD4 count ≤ 350 and/or RPR titer ≥ 1:32 were tested for neurosyphilis by performing lumbar puncture (LP) regardless of their neurological symptoms.[17]

Statistical Analysis

The data are presented as descriptive statistics including mean, standard deviation (SD), quartile (25th quartile, median and 75th quartile) and frequency values in tables. The normal distribution of the numerical data was examined using the Shapiro-Wilk test. The patients who were included in the study were divided into two groups as TPHA-positive and TPHA-negative, and these two groups were compared using Mann-Whitney U test in terms of their numerical demographic characteristics, and their categorical data were compared using the Fisher-Freeman-Halton exact test. The level of statistical significance was accepted as $p<0.05$, and SPSS (version 23) was used for the analysis.

Results

The study included 474 patients living with HIV. Of the patients, 429 (90.5%) were male and 206 (47.9%) of the male patients were men who have sex with men (MSM) (Table 1). The median (IQR) age of the patients was 37 (30-47). The

Table 1. Demographic characteristics of all patients included in the study

Variable	n	%
Sex		
Female	45	9.5
Male	429	90.5
Education Level		
Primary school	43	9.1
Secondary School	48	10.1
High school	107	22.6
University	276	58.2
MSM		
No	224	52.1
Yes	206	47.9
Marital Status		
Married	162	34.2
Single	308	65.0
Divorced	4	0.8
Using Condom		
No	110	23.3
Yes	363	76.7
Syphilis Exposure		
No	331	69.8
Yes	143	30.2

MSM: men who have sex with men.

median follow-up duration of the patients was 48 (24-72) months (Table 2). Three hundred and sixty-three (76.7%) patients used condoms routinely, and 276 (58.2%) were university graduates. The syphilis coinfection rate in our participants was 30.2% (143/474) (Table 1). The median (IQR) CD4 T lymphocyte count at the first visit was 432 (265.5-599.0) cell/mm3, and the median (IQR) HIV RNA value was 154849.5 (30441.7-637175.0) IU/ml. The patients' median (IQR) TPHA value was 1280 (160-2560). RPR negativity and TPHA positivity were found in 4 of the patients, who were accepted as previous infections (Table 2). The RPR titers were found to be 1:2 in 48 (48/143, 33.6%) patients. The RPR titer distributions of the patients coinfected with syphilis are presented in Table 3.

Table 2. Demographic characteristics of all patients included in the study

	n	Median (IQR)
Age	474	37.0 (30.0-47.0)
Duration of follow-up (months)	473	48.0 (24.0-72.0)
RPR (%)	139 (29.32)	4.0 (2.0-32.0)
TPHA (%)	143 (30.2)	1280.0 (160.0-2560.0)
CD4 at diagnosis	473	432.0
CD4 at last patient visit	474	689.0
HIV RNA at diagnosis	474	154849.5
HIV RNA at last patient visit	473	0

RPR: rapid plasma reagin; TPHA: *Treponema pallidum* hemagglutination assay; HIV RNA, human immunodeficiency virus ribonucleic acid.

Table 3. RPR titers in patients with syphilis coinfection

	TPHA positive	
	n	%
RPR titer		
1	1	0.7
2	48	33.6
4	26	18.2
8	15	10.5
16	8	5.6
32	11	7.7
56	2	1.4
64	15	10.5
128	8	5.6
256	2	1.4
512	3	2.1
Negative	4	2.8
Total	143	100.0

RPR; rapid plasma reagin; TPHA; *Treponema pallidum* hemagglutination assay.

Eighty (80/474, 16.9%) of the patients were coinfected with syphilis at the time of their HIV diagnosis. Sixty-three (63/474, 13.3%) patients got infected with syphilis in a median (IQR) time of 60 (36-84) months into their HIV follow-up and treatment.

There was no statistically significant relationship between the TPHA results of the patients and their age and education level (p-values: 0.119 and 0.699, respectively). Being men (99.3%) (p<0.001), being MSM (57%) (p=0.008) and being single (75.5%) (p=0.007) were found to be statistically significant predictors of syphilis exposure. Regular condom use was inversely correlated with syphilis coinfection (p=0.002). The CD4 values of 94 (94/143, 65.7%) patients with syphilis were >350 cell/mm^3, while the CD4 values were ≤ 350 cell/mm^3 in 49 (49/143, 34.3%) patients (Table 4). Ten (10/143, 7.0%) patients, of whom four had neurological symptoms and six had no neurological symptoms but CD4 count ≤ 350 and/or RPR ≥ 1:32 titer, were diagnosed as neurosyphilis by lumbar puncture findings, and they received appropriate treatment. While seven (7/143, 4.9%) patients who presented in the secondary period had skin rashes, and two (2/143, 1.4%) patients who presented in the primary period had oral lesions, 134 (134/143, 93.7%) patients were asymptomatic and in the latent period.

Discussion

It was found in this study that the *T. pallidum* infection rate among the PLHIV who were monitored in our clinic was approximately one over three. Almost all patients with syphilis coinfection were male, and more than half of them were MSM. Studies conducted around the world have reported the rate of HIV and syphilis coinfection between 6.21% and 46.5%. This rate was 6.21% in Singapore, 8-25% in Turkey, 25% in Mexico, 46.5% in Taiwan, 16.42% in Morocco, 18.4% in Brazil, 16.1% in Thailand, and 10% in Ghana.[5-11,18-21]

Syphilis has reemerged as a public health problem especially in bisexuals and MSM, which are high-risk groups. MSM are also the key population for HIV infection. Similarly, various studies in the literature have determined that coinfection rates are the highest among male individuals and MSM.[5,7,9,20]

This cohort study revealed that more than half of the patients with syphilis were diagnosed as syphilis together with HIV diagnosis, and almost half of them were TPHA-negative at the beginning but were detected to have syphilis during their follow-up. Patients infected with HIV should be tested for syphilis exposure during the follow-up of their infection.

The correct use of condoms prevents sexually transmitted diseases.[22] In our study, the rates of syphilis exposure

Table 4. Distribution of TPHA-negative and TPHA-positive patients based on demographic characteristics

	TPHA negative (n=331)		TPHA positive (n=143)		
	n	%	n	%	P
Age group					
18-25	31	9.4	13	9.1	0.221
26-45	201	60.7	98	68.5	
46 and older	99	29.9	32	22.4	
Sex					
Female	44[a]	13.3	1[b]	0.7	<0.001
Male	287[a]	86.7	142[b]	99.3	
Education Level					
Primary school	27[a]	8.2	16[a]	11.2	0.509
Secondary School	35[a]	10.6	13[a]	9.1	
High school	71[a]	21.5	36[a]	25.2	
University	198[a]	59.8	78[a]	54.5	
MSM					
No	163[a]	56.6	61[b]	43.0	0.008
Yes	125[a]	43.4	81[b]	57.0	
Marital Status					
Married	128[a]	38.7	34[b]	23.8	0.007
Single	200[a]	60.4	108[b]	75.5	
Divorced	3[a]	0.9	1[a]	0.7	
Using Condom					
No	64[a]	19.3	46[b]	32.2	0.002
Yes	267[a]	80.7	97[b]	67.8	
CD4 count at diagnosis					
<=350	126	38.1	49	34.3	0.451
>350	205	61.9	94	65.7	

[a]: significantly different from b, [b]: significantly different from a. MSM, men who have sex with men.

among the patients who did not use condoms were significantly higher. In general, syphilis is sexually transmitted with direct skin contact from active primary and secondary lesions. Syphilis can be transmitted with lesions in the penis, groin, mouth and anus that cannot be covered with a condom.[23] Studies have shown that oral sex, which is regarded as a safer sexual activity, is the most effective route of infection.[4,24] Patients infected with HIV continue their risky sexual behaviors, thus easing the spread of other sexually transmitted diseases, especially syphilis. Safe sex, avoiding risky sexual behaviors, and educating and informing patients are the most effective ways for controlling these coinfection cases.

While Riley et al.[25] found that syphilis infection occurs in PLHIV most frequently between the ages of 25 and 44, Mata Marin et al.[10] reported that it occurs between the ages of 30 and 39, and Asade- Beideko et al.[21] stated that it occurs between the ages of 20 and 39. The fact that the young age group has more sexual activity, and their tendency to find multiple partners on the internet is higher than the elderly population may play a role in increasing their syphilis exposure. There was no statistically significant difference between the TPHA-positive and TPHA-negative patients in the sample of this study in terms of their age distributions.

HIV and syphilis coinfection cases are a dangerous combination. Numerous chancres can be observed in the primary period, but the infection can also progress asymptomatically. The disease is more common in the secondary stage and causes more immune activity. This stage may progress aggressively, and early neurological involvement may develop.[4,26] In this study, 10 patients were regarded as neurosyphilis and treated accordingly.

CD4 count decreases in the presence of primary and secondary syphilis coinfection while viral load increases, thus causing the progression of HIV infection. This situation is reversible after the treatment of the syphilis infection.[13,27] Among the patients in this study, two were in the primary

period, seven were in the secondary period, and most of them were in the latent period. None of the patients were found to have CD4 T lymphocyte decrease and viral load increase since their diagnoses were made mostly in the latent period during their follow-up.

Our study is limited because it is retrospective nature, however, we think that our study may contribute to the literature by demonstrating the syphilis seroprevalence HIV-positive patients.

In conclusion, this study revealed that the prevalence of syphilis among PLHIV was one-third. It was also found that the infection rates were higher among men, MSM and patients who did not use condoms regularly. The risk factors of the disease should be determined, especially young individuals should be informed about sexually transmitted diseases, their effects and preventive ways, and new social strategies about this topic should be developed. Raising awareness about syphilis among individuals infected with HIV and about HIV among individuals infected with syphilis and carrying out screenings in routine follow-ups is highly important for the early diagnosis and treatment of both diseases and for taking the rates of their spread under control.

Disclosures

Ethics Committee Approval: The study protocol was approved by Medeniyet University Goztepe Training and Research Hospital Ethics Committee with 19/02/2020 dated and 2020/0122 numbered decision.

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Conflict of Interest: None declared.

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