Research Article

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Title: Syphilis coinfection in individuals living with HIV: tertiary university hospital data.

Short title: Syphilis coinfection with HIV.

Abstract

Purpose: This study aimed to examine the coinfection of syphilis in HIV-positive individuals and the epidemiological and clinical characteristics of these patients.

Material and methods: Our study was conducted in Çanakkale Onsekiz Mart University, between 13.02.2018 and 13.02.2024, in 26 patients with clinically and laboratory-confirmed syphilis co-infection among 142 HIV/AIDS patients who were followed up and confirmed in the infectious diseases and clinical microbiology outpatient clinic.

Results: A total of 142 HIV positive and 26 (18.3%) syphilis coinfected patients between the ages of 17-77 were included in the study. The mean ages of the infected and syphilis coinfected patients were 39.1 and 41.07, respectively. Six (23%) of the coinfected patients were married, the remaining 14 (53.8%) were single or divorced, five had multiple partners; 20 (77%) were heterosexual, four (15%) were men who have sex with men (MSM), and two (8%) were bisexual. Simultaneous HIV/syphilis positivity was detected in 14 (54%) of the coinfected patients at the time of diagnosis, while 7 (27%) were detected during the HIV treatment follow-up period, and 5 (19%) were detected before HIV diagnosis. Of the patients with coinfection, five (19.2%) had primary syphilis, 10 (38.5%) had latent syphilis, and 11 (42.3%) had secondary syphilis at the time of diagnosis. Twenty-two (85%) of the patients had been diagnosed and treated for syphilis only once, while the remaining (15%) had received two or more treatments.

Conclusions: The prevalence of syphilis coinfection and reinfection in patients was 18.3% and 15%, respectively. In cases of coinfection, male gender, alcohol and drug consumption, being MSM, irregular lifestyles, and sexual habits were found to be effective. It is important to conduct screening for syphilis and other sexually transmitted diseases (STDs) in HIV-infected patients. Providing psychiatric support to these patients in organizing their life plans is also very important for preventing HIV transmission and syphilis coinfection.

Keywords: Syphilis, HIV, coinfection.

Makale başlığı: HIV ile yaşayan bireylerde sifiliz eş enfeksiyonu: üçüncü basamak üniversite hastanesi verileri.

Kısa başlık: HIV-sfiliz koenfeksiyonu.

Öz

Amaç: Bu çalışmada HIV ile infekte bireylerde sifilizin koenfeksiyonunun varlığı ve bu hastaların epidemiyolojik ve klinik özelliklerinin incelenmesini amaçladık.

Gereç ve yöntem: Çalışmamız 13.02.2018-13.02.2024 tarihleri arasında Çanakkale Onsekiz Mart Üniversitesi Hastanesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji polikliniğinde takip edilen ve tanısı doğrulanan 142 HIV/AIDS hastası arasından klinik ve laboratuvar olarak doğrulanmış sifiliz koenfeksiyonu olan 26 hastada gerçekleştirildi.

Bulgular: Çalışmaya yaşları 17-77 arasında değişen 142 HIV pozitif ve 26 (18,3%) sifiliz koenfekte hasta dahil edildi. Enfekte ve sifiliz koenfekte hastaların yaş ortalamaları sırasıyla 39,1 ve 41,07 idi. Koenfekte hastaların altısı (23%) evliyken, kalan 14'ü (53,8%) bekar veya boşanmış, beşi multipartnerli; 20'si (77%) heteroseksüel, dördü (15%) hasta erkeklerle seks yapan erkekti (men who have sex with men – MSM), ikisi (8%) biseksüeldi. Koenfekte hastaların 14'ünde (54%) eş zamanlı HIV/sifiliz pozitifliği tanı anında tespit edilirken, 7'si (27%) HIV tedavi-takip sürecinde ve 5'i (19%) HIV tanısı öncesinde tanı almıştı. Koenfekte hastaların beşinde (19,2%) tanı anında primer, 10'unda (38,5%) latent ve 11'inde (42,3%) tanı anında sekonder sifiliz vardı. Hastaların 22'sine (85%) sadece bir kez sifiliz tanısı konulmuş ve tedavi edilmişken, kalan (15%) hastalar iki veya daha fazla tedavi almıştı.

Sonuç: Hastalarda sifiliz koenfeksiyonu ve reenfeksiyon prevalansı sırasıyla 18,3% ve 15% idi. Koenfekte hastalarda erkek cinsiyet, alkol ve uyuşturucu tüketimi, erkeklerle seks yapan erkek olmak (MSM), düzensiz yaşam tarzı ve cinsel alışkanlıkların etkili olduğu bulundu. HIV enfeksiyonlu hastalarda sifiliz ve diğer cinsel yolla bulaşan hastalıklar (CYBH) için tarama yapmak önemlidir. Bu hastalara yaşam planlarını düzenlemeleri konusunda psikiyatrik destek sağlamak HIV bulaşmasını ve sifiliz koenfeksiyonunu önlemek için çok önemlidir.

Anahtar kelimeler: Sifiliz, HIV, koenfeksiyon.

Introduction

Sexually transmitted diseases, such as HIV and syphilis, have shown an increasing trend worldwide. The most common method of transmission is heterosexual sexual intercourse. In addition, transmission routes, such as homosexual/bisexual sexual intercourse, intravenous drug use, infected blood transfusion, sharp object injuries, and transmission from mother to baby, are also known. Although HIV-positive patients receive antiretroviral therapy, the continuation of risky behaviors leads to an increase in other sexually transmitted diseases [1].

Syphilis is a sexually transmitted systemic infectious disease caused by a bacterium from the spirochete family, *Treponema pallidum* and is a major public health problem worldwide [2]. There has been an increase in syphilis cases in Türkiye in recent years, with 3533 cases detected as of December 31, 2022 [3].

Syphilis and HIV are both sexually transmitted, and co-infection often occur in men sex who have with man (MSM). Individuals who have recently been diagnosed with HIV are at higher risk of developing syphilis due to overlapping risk behaviors, such as having unprotected sexual activity. HIV infection has various effects on the onset, diagnosis, disease progression, and treatment of syphilis. While HIV infection negatively affects the prognosis of syphilis, genital ulcers observed in the course of syphilis may also increase the risk of HIV transmission [4].

HIV, anti-HIV therapies and psychosocial stressors in HIV disease lead to psychiatric morbidity like depression throughout the disease course. Depressive symptoms increases progress of the disease [5]. As a result, patients postpone application to a health institution.

Especially among MSM, there is a high rate of HIV/syphilis co-infection due to the common transmission routes of HIV and syphilis and the increased infectiousness of one in the presence of the other [6]. Therefore, detecting the seroprevalence and risk factors of syphilis in HIV-infected individuals will draw a road map in preventing the spread of these infections. Considering the common transmission routes and increasing importance of Syphilis and HIV, our study aimed to investigate the presence of syphilis coinfection in individuals with HIV infection and analyze the risk factors, prognostic features and clinical and laboratory data of these patients.

Material and methods

Our study was carried out in patients coinfected with HIV and Syphilis, whose diagnosis was confirmed and followed up by the Çanakkale Onsekiz Mart University Faculty of Medicine, Infectious Diseases and Clinical Microbiology Department, between

13.02.2018 and 13.02.2024. Retrospective data, including demographic and clinical/laboratory information, were collected from medical records obtained from the hospital's doctor and laboratory information system, including age, sex, HIV transmission route, coinfection with hepatitis B virus (HBV), and coinfection with hepatitis C virus (HCV).

HIV screening in serum samples was performed by ELISA (Architect-i2000-ABBOTT-USA), and recurrent reactive samples were confirmed by immunoblotting in the Turkish Public Health Institution Reference Laboratory. In the Western blot / “line immunoassay” test, in accordance with the recommendations of the CDC and the World Health Organization [7], at least two envelope protein bands (sgp120/gp41 or sgp105, gp36) or at least one envelope protein band (sgp120/gp41 or sgp105, gp36) with the presence of p24 antigen band was accepted as a confirmatory criterion for the diagnosis. Detection of bands other than those specified was considered indeterminate, and absence of a band was considered negative [8].

For serological syphilis diagnosis, the reverse algorithm was followed between 13.02.2018 and 13.02.2024, and all serum samples were tested as a non-treponemal test using VDRL (Trepolipin, Tulip Diagnostic, India) and RPR (Carbogen, Tulip Diagnostic, İndia), and as a treponemal test, TPHA (Spinreact, Girona, Spain). For both tests, the manufacturer's recommendations were followed. Serum titers detected at 1/80 and above in the TPHA test were considered positive.

Primary syphilis: cases characterized by the presence of one or more ulcers (chancres) with positive serological tests. Secondary syphilis is characterized by characteristic lesions (localized or mucocutaneous) accompanied by generalized lymphadenopathy, often without the presence of a primary chancre), with positive serological tests. Latent syphilis: cases detected with reactive non-treponemal and treponemal tests without any clinical signs or symptoms or with a fourfold increase in non-treponemal test titers compared to previously reported non-treponemal tests, or with a significant increase in titers according to the latest non-treponemal tests in the presence of a history of syphilis treatment. Latent syphilis is categorized into early latent (less than one year), late latent (more than one year), and indeterminate, based on the duration of infection. The patients were staged according to these definitions.

The study was approved by the Clinical Research Ethics Committee of Çanakkale Onsekiz Mart University Medical school by protocol number 2024-07-06 and date: 24.07.2024.

Since our study was conducted retrospectively based on patient anamnesis files and hospital information system physician notes, informed consent was not obtained from the patients. There had been no face-to-face contact with the patients during the study.

Results

One hundred forty two patients diagnosed with HIV tested for syphilis, and 26 (18.3%) of them were coinfected. The average age of HIV and coinfected patients was found to be 39.1, ranging from 17 to 77 years old and 41.07, ranging from 23 to 61 years. 90.1% of HIV patients (n=128) and 100% (n=26) of coinfected patients were male (Table 1). Patients who tested negative for TPHA were considered to have never encountered syphilis during their lifetime. Positive results detected at a dilution of 1/80 or higher in the TPHA test were considered statistically significant. All HIV-syphilis coinfected patients were TPHA-positive. In TPHA positive patients, 61.5% (n=16) of them were RPR, 76.9% (n=20) of them were VDRL positive (Figure 1). The findings obtained in the study include the demographic and clinical characteristics of the coinfected patients shown in Table 2.

While all primary and secondary syphilis cases were VDRL positive; in latent cases positivity was 5 (45.4%) at the time of diagnosis. When the VDRL dynamics of these cases before and after treatment were examined, a decrease and disappearance of the VDRL titer was observed after treatment. In all cases, the VDRL was negative for at least 12th month after treatment. When HIV-syphilis co-infected patients were screened for HBV and HCV, HBsAg positivity was detected in two patients, isolated anti-Hbc IgG positivity was detected in one patient and two patients were anti-HCV positive.

While 18 (69.2%) patients had no comorbidities, the remaining 8 (31.8%) had additional conditions such as diabetes, hypertension, depression, asthma, hepatitis B, and C. Among the patients, 17 (60.7%) had a history of alcohol consumption, 5 (19.2%) had a history of drug addiction, and 1 had received immunosuppressive agents due to non-Hodgkin lymphoma. Six (23%) of the coinfected patients were married, while the remaining 14 (53.8%) were single or divorced; 20 (77%) were heterosexual, four (15%) were men who have sex with men (MSM), and two (8%) were bisexual. Regarding the transmission routes of syphilis, one patient had a history of dental procedures in prison, two had a common history of using personal care items, and one had a history of hospitalization in Tanzania, two had iv drug history, while the majority (n=20, 77%) had a history of unprotected sexual intercourse. As a matter of fact, when the demographic data of the patients were examined, it was seen that one was a sex worker, two were prisoners, five were drug addicts, one was an immigrant, three had a history of working abroad, and all patients were male.

While 14 (54%) of the co-infected patients were simultaneously HIV/syphilis positive, seven (27%) were found to be syphilis positive during the HIV treatment follow-

up period, and five (19%) were positive to be syphilis positive before HIV diagnosis (Figure 2).

Among those with coinfection, 5 (19.2%) had primary syphilis, 11 (42.3%) secondary syphilis, and 10 (38.5%) latent syphilis (Figure 3). Genital chancre was the common finding in primary syphilis cases, whereas rash and lymphadenopathy were the most common findings in secondary syphilis. One patient had ocular syphilis infection. While 24 patients (88.8%) were treated with 2.4 million units of benzathine penicillin G once a week for 3 weeks; one patient received doxycycline due to penicillin allergy, and another received ceftriaxone therapy due to ocular syphilis for 14 days.

Twenty two (85%) patients had received syphilis diagnosis and treatment only once, while the remaining (15%) had received two or more treatments. When the partners were questioned whether they had syphilis, it was seen that partner of four (15%) had syphilis as known. HIV-positive patients received antiretroviral treatments between 2 and 149 months (average, 64 months). While twenty-four (92%) patients had been receiving HIV treatment for more than a year, two patients were diagnosed in the last 2 months. Thirteen of the patients received bictegravir, emtricitabine, and tenofovir alafenamide; four patients received abacavir, lamivudine, dolutegravir; 4 patients lamivudine, dolutegravir; 3 patients dolutegravir, emtricitabine, and tenofovir disoproxil; and two patients received elvitegravir, emtricitabine, and tenofovir alafenamide combination therapy. After at least 12 months follow-up, in the last examination of patients receiving regular antiretroviral treatments, HIV RNA positivity was detected in four (22.2%).

While none of the co-infected patients had a CD4 count below 200 during syphilis infection, the control CD4 count after treatment was above 400 and only four patient's mean CD4 count of 202.

Discussion

In a multicenter study conducted in our country, the HIV/syphilis coinfection rate was found to be 8% [9] this rate was found to be between 1-25% in the literature review [10]. In 2022 Türkiye statistics, most patients diagnosed with syphilis were male (81.5%) and between the ages of 25-29 [11]. Müderris et al. [12] stated that, all patients except one were male among HIV/syphilis coinfected patients, and more than 90% of the were over 25 years of age. Consistent with the literature, in our study, HIV-syphilis comorbidity was found to be 18% in HIV patients, and all patients were male (100%) between the ages of 23-61 (mean: 41.07).

The coexistence of HIV infection and syphilis has been increasing worldwide in recent years, especially among MSM [13]. Fan et al. [14] stated in his meta-analysis

published by 2021, that 40.1% of HIV/Syphilis co-infected patients was receiving ART and 42.5% of them was MSM. In our study, all patients were receiving ART and five patients had multiple partners and four were MSM and two were bisexual.

Most patients diagnosed with HIV between 1985 and 08 November 2023 were men (81.4%) and Turkish citizen (83.1%) [15]. In our study, only one patient was an immigrant and the rest were Turkish citizens (96%). Although no mortality was observed in our patients during an average of 6 years of follow-up, it is taken into consideration that this rate may change in longer-term follow-up.

Co-transmission of T. pallidum and HIV may be due to the risky behavior of patients, such as unprotected intercourse and multiple partnerships. Therefore, in addition to applying a syphilis screening test to patients newly diagnosed with HIV infection, syphilis screening tests should be repeated during routine follow-up of patients with risky behavior or suspicious clinical findings [16, 17]. In our study, six patients were married, and all patients had a history of risky sexual behavior. Seven patients (27%) catched syphilis during HIV treatment and follow-up.

Sarıgül et al. [17] stated that, 25% of 384 HIV-positive patients had HIV/syphilis coinfection and 94% of these patients had positive RPR and TPHA tests. In our study, 77% of patients had VDRL and TPHA, 61% patients had RPR and TPHA positivity, respectively.

Remera et al. [18] stated that, HIV and hepatitis B virus coinfection found 0·5%, whereas HIV and hepatitis C coinfection was 0·1% and no coinfection for any three viruses was observed. In our study, there were 2 separate patients with hepatitis B (7.7%) and C (7.7%) coinfected, and 5 (19%) of them had urethritis. Our high rate might be due to the low total number of patients. We believe that the reason for our high rate is that Türkiye is in the medium-endemicity region in terms of hepatitis.

Recently, a significant increase in the number of primary and secondary syphilis cases has been reported worldwide. According to CDC data, approximately half of homosexual men with primary and secondary syphilis are infected with HIV. Studies have shown that the symptoms of secondary syphilis appear more frequently during the same period as chancres in patients with HIV infection [19]. In our study, five (19.2%) had primary syphilis, 10 (38.5%) had latent syphilis, and 11 (42.3%) had secondary syphilis. While the symptoms of syphilis are very diverse, the untreated disease passes into the latent phase over time, and the symptoms disappear, making it difficult to combat the disease and seems to be a significant problem. Although the secondary syphilis patient group was the most frequently admitted patient group in our study (42.3%), the high number of patients in the latent phase (38.5%) attracted our attention.

The most common manifestation of syphilis in the eye is uveitis, which can occur at any stage of infection. Although most patients recover well with penicillin treatment, some may develop visual loss due to macular edema and endarteritis, causing retinal ischemia [20, 21]. After penicillin treatment, 67% of patients experienced improved vision, with 92% rate reduced inflammatory signs. However, despite treatment, relapse of ocular diseases may still occur [9, 22]. In this study, only one patient developed ocular syphilis during the second syphilis stage, and no vision loss was observed during the post-treatment follow-up.

In HIV/syphilis co-infection, HIV is more likely to fail syphilis treatment, and co-infection leads to profound neurocognitive impairment [23]. In our study, no neurological findings other than depression (n=5,19%) were observed. In addition, in the only case of ocular syphilis, there was no neurological involvement. In our study, no treatment failure was observed for syphilis.

Fan et al. [14] stated that syphilis reinfection rate was 7% in 7 years. In our study, four patients (15%) received syphilis treatment multiple times. The higher reinfection rate in our study than that reported in the literature was associated with the small number of patients.

The main limitation of the study was that patients tended to give hesitant answers when questioning sexual history in outpatient clinics.

In our study, syphilis coinfection and reinfection rates in HIV patients found to be 18% and 15%, respectively. We observed that our patients applied to health institutions, especially in the late stages of syphilis, or received their diagnosis late. This situation is thought to be due to reasons such as lack of education and sexual stigma. Considering the importance of early diagnosis in terms of prognosis and public health, planning educational activities aimed at increasing the level of sexual knowledge in our country and increasing the number and functionality of Voluntary Counseling and Testing Centers (VTCs) reveals the importance of approaches.

Even though 46% of the patients were coinfected with HIV or syphilis after the first diagnosis and the fact that approximately 1/3 of the patients diagnosed with syphilis in the latent stage, as well as the 19% presence of concurrent urethritis, made us think that the patients continued their unprotected sexual habits and they did not avoid risky contact.

In addition, the development of mood disorders, such as depression, in this group of patients, who are mostly unmarried (n=20.77%) and do not live a regular life, also contributes to the course of the disease. Considering the increase in morbidity and mortality that may be caused by these disorders, as a natural consequence of the disease by both the patient and the physician normalized, ignored or overlooked during the disease

process, the patient's cognitive and psychosocial status, mental complaints should be routinely questioned independent of the infection. However, under outpatient clinic conditions, our patients may not accurately express information about their psychosocial status or sexual preferences. Considering the large number and diversity of outpatient clinic patients in our country, examining this patient group in seperate clinic rooms and on different days reserved for HIV patients will yield more accurate results in terms of correctly identifying transmission routes and analyzing psychosocial and sexual problems that may adversely affect the course of the disease.

Screening for syphilis in HIV-infected patients, planning training for sexually transmitted diseases with treatment, providing psychological support, and advising patients to organize their life plans are very important to prevent syphilis and HIV transmission.

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Conflict of interests: The authors have no conflict of interest to declare.

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Main Points: Our analysis about HIV and syphilis coinfected patients whom had received a secondary sexually transmitted disease (STD) diagnosis after receiving their first STD diagnosis made us think that the patients continued their unprotected sexual habits and they did not avoid risky contact. We also found that all coinfected patients in our study were male.

Not being married and having multi-partner sexual life or an irregular work contributes to the course of the disease.

The main reason why these patients applied to healthcare institutions late or received their diagnosis late situation is thought to be due to reasons such as lack of education and sexual stigma.

Screening for syphilis in HIV-infected patients, planning training for sexually transmitted diseases with treatment, providing psychological support, and advising patients to organize their life plans are very important to prevent syphilis and HIV transmission.

Table 1. Distribution and characteristics of all patients

	Total number of patients (n)	Mean Age	Gender
HIV-Positive	142	39.1 (17-77)	Male:128 (90.1%) Female:14 (9.9%)
HIV+ Syphilis	26	41.07 (23-61)	Male:26

Table 2. Distribution and characteristics of HIV/Syphilis coinfected patients

	Total number of patients(n)	Percent (%)
Gender/ Male	26	100
MSM	4	15
Bisexual	2	8
Married	6	23
Multiple partners	5	19
Alcohol consumption	17	74
Drug Addicition	5	19
No-Comorbid diseases	18	69
Urethritis	5	19
Depression	5	19
Hypertension	4	15
DM	3	11
Hepatitis C	2	8
Hepatitis B	2	8
Non-Hodgkin lymphoma	1	4
Extra pulmoner tbc	1	4
Asthma	1	4
Prisoner	2	8
Refugee	1	4
sex worker	1	4

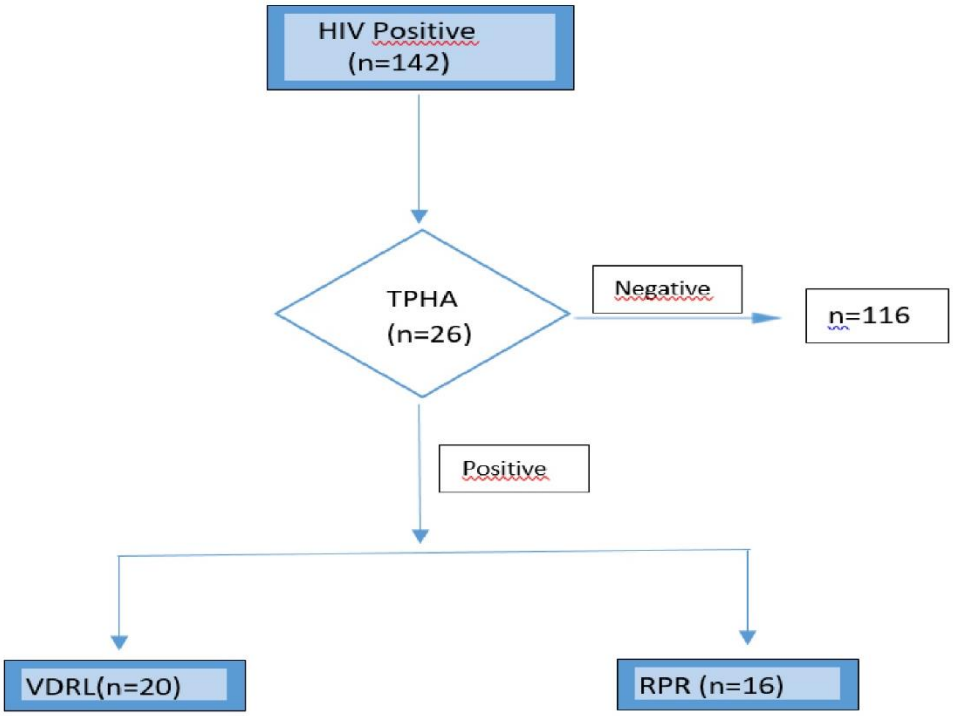

Figure 1. Syphilis serological test results of all patients

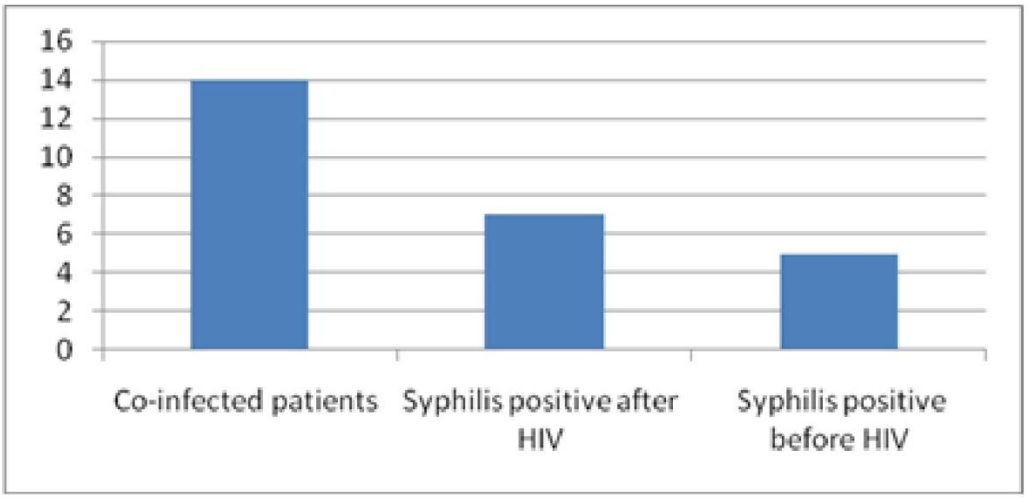

Figure 2. Separation of patients according to the order of coinfection

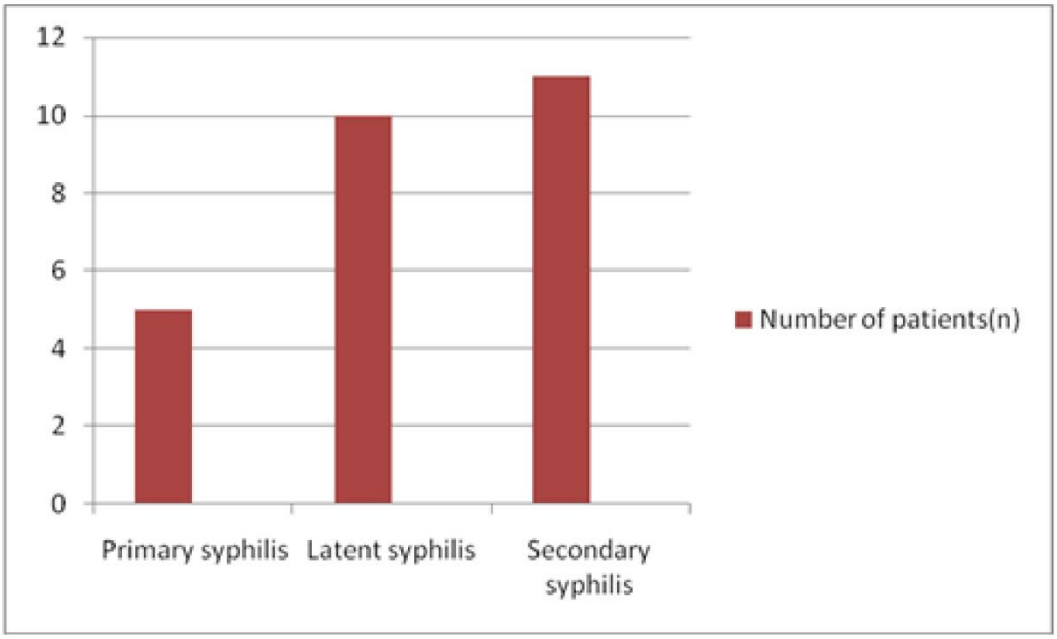

Figure 3. Clinical staging of syphilis in coinfected patients

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