Neurosyphilis with Ocular Involvement in a Patient with Newly Diagnosed Human Immunodeficiency Virus (HIV) Infection: A Case Report

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Abstract

Introduction: Syphilis is a chronic systemic infection caused by *Treponema pallidum* sub-species *pallidum*. Syphilis, by itself, already has a varied clinical presentation depending on the stage, earning its moniker as "the great imitator". In a patient without HIV infection, untreated syphilis presents as a chronic infection with primary, secondary, latent, and tertiary stages. With the emergence of the AIDS pandemic, HIV co-infection may significantly alter the clinical presentation of syphilis. This is a case of a patient with neurosyphilis with overlapping primary and secondary syphilis.

Case Presentation: This is a case of a 34-year-old Filipino male who came in due to blurring of vision. The patient's illness started six months prior to admission, when he noted the appearance of a painless, non-pruritic, solitary ulcer with erosions on his penis. A month after, he started to have progressive blurring of vision. In the interim, erythematous, scaly plaques appeared on the dorsal aspect of both hands and feet, and on the tip of the nose, with associated thinning of hair on the scalp and eyebrows. The skin and penile lesions eventually increased in size and number. The examination of the pupils showed a 6 mm right pupil, non-reactive to light, and a 2 mm left pupil which was minimally reactive to light and constricts upon accommodation. The diagnosis of syphilis was confirmed by a reactive serum Rapid Plasma Reagin at 1:64 dilution, and a reactive serum Treponemal Enzyme Immunoassay. HIV screening was also reactive, with a CD4+ cell count of 15 cells/μL. Ophthalmologic findings were consistent with panuveitis. Skin punch biopsy revealed lichenoid and interstitial dermatitis with which syphilis was highly considered. Cranial CT imaging showed mild cerebral atrophy. Lumbar tap revealed a colorless, clear cerebrospinal fluid, with lymphocytic pleocytosis, normal protein, decreased glucose, and a reactive CSF RPR. The patient was given intravenous penicillin G 3 million units every 4 hours for 14 days, together with ophthalmic medications (prednisolone, levofloxacin, and atropine ophthalmic drops). He was also started on antiretroviral therapy. Prior to discharge, the patient was noted to have improved vision, skin lesions were significantly improved, and he was advised for close monitoring as outpatient.

Conclusion: Through this case, it was elaborated that with HIV co-infection, syphilis may present atypically—with multiple, persistent, primary lesions; with overlapping of the stages, and increased frequency of neurosyphilis presenting early into the infection.

Keywords: syphilis; neurosyphilis; ocular syphilis; HIV; HIV co-infection

Introduction

Syphilis is a chronic, systemic disease caused by *Treponema pallidum* sub-species *pallidum*. It is usually sexually transmitted, and is classified into different stages. The primary stage is associated with a primary lesion known as the chancre, a firm, nontender ulcer

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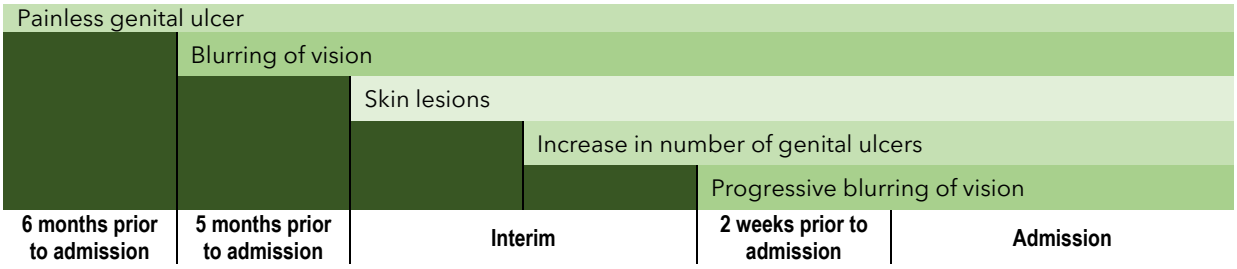


Figure 1. Timeline of the patient's history of present illness

located at the site of inoculation. If left untreated, it is then followed by a secondary stage associated with generalized mucocutaneous lesions and generalized lymphadenopathy. The infection, if it remains untreated, then enters a period of latency, lasting for years. In the pre-antibiotic era, one-third of untreated patients developed tertiary syphilis after 15-30 years, presenting with disfiguring mucocutaneous, skeletal, or parenchymal lesions known as gumma; aortitis; or late central nervous system (CNS) manifestations. CNS involvement (neurosyphilis) may occur in any stage of syphilis, presenting early, or later in the course of infection.[1,2]

Since the advent of antibiotics, the complications of syphilis are less commonly seen as compared to the pre-antibiotic era. However, with the emergence of the acquired immunodeficiency syndrome (AIDS) pandemic, syphilis and HIV became strongly linked with one another. HIV co-infection may significantly alter the clinical presentation of syphilis. Visual disturbances, headache, uncontrolled viremia, and a CD4+ cell count of 500 cells/μL or less were predictors of neurosyphilis in HIV-infected patients with early syphilis.[10]

In this report, we present a patient with HIV and neurosyphilis with overlapping primary and secondary syphilis.

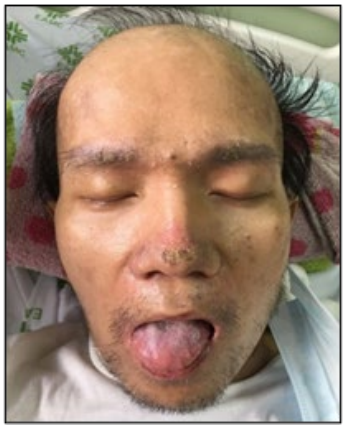
According to the Centers for Disease Control and Prevention (CDC), in 2019, 129,813 cases of all stages of syphilis, were reported, including 38,992 cases of primary and secondary syphilis, the most infectious stages of the disease. Men who have sex with men (MSM) and men who have sex with men and women (MSMW) accounted for 47% of all primary and secondary syphilis cases. In the United States, approximately half of MSM with primary and secondary syphilis were also HIV co-infected.[30, 31] In the Philippines, there were 2,818 newly confirmed HIV positive individuals reported to the HIV/AIDS & ART Registry of the Philippines (HARP) from January to March 2020. Seventeen percent (473) had clinical manifestations of advanced HIV infection at the time of testing.[32] However, local epidemiologic data regarding syphilis with HIV co-infection is still lacking.

Case Presentation

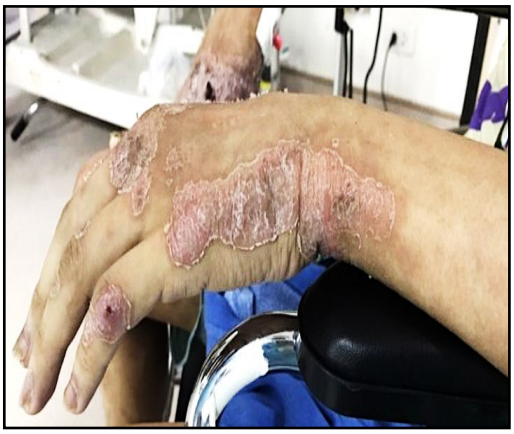
This is a case of a 34-year-old Filipino male who came in due to blurring of vision of both eyes. The patient's illness started six months prior to admission when the patient noted the appearance of a painless, non-pruritic, solitary ulcer with erosions on the glans penis with no associated bleeding or penile discharge (*Figure 1*). A month after, he started to have blurring of vision. In the interim, the patient noted the appearance of erythematous, scaly plaques on the dorsal aspect of both hands and feet, and on the tip of the nose, with associated thinning of hair on the scalp and eyebrows. The skin and penile lesions previously noted by the patient has increased in size and number, and involved both upper and lower extremities. Two weeks prior to admission, the patient noted progressive blurring of vision, with the patient depending on assistance from others for his daily activities.

The patient has no known comorbidities. He denies a prior history of sexually transmitted diseases. He has no previous hospitalization, surgery, and blood transfusion. He is a non-smoker, occasional alcoholic drinker, and worked as a cook abroad. The patient is bisexual, with multiple male partners, and doesn't use protective barriers. He denies illicit drug use.

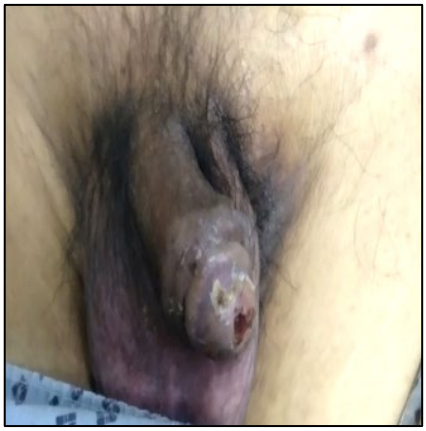
Upon physical examination, vital signs were stable. Pertinent findings were as follows: (a) multiple, well-defined, irregularly shaped, erythematous to hyperpigmented plaques with crusting on the face, dorsal aspect of both hands, dorsal and plantar aspect of both feet; (b) multiple, well-defined, irregularly shaped, erythematous to hyperpigmented, painless ulcers on the glans penis and scrotum; (c) yellow to brownish discoloration and hyperkeratosis with subungual debris on the fingernails and toenails; (d) diffuse hair loss on the fronto-parietal area with thinning of eyebrows; (e) yellowish scales over the eyebrows with erythema; (f) erythematous plaques with yellowish crusting on the tip of the nose; (g) multiple, white patches on the buccal mucosa and tongue; (h) multiple, firm, movable, non-tender, bilateral cervical lymphadenopathy, largest of which measures approximately 2 x 2 cm; (i) visual acuity was designated as no hand movement, poor light projection on the right eye, and with hand movement, poor light projection on the left eye; (j) examination of the pupils showed a 6 mm right pupil which was non-reactive to light but constricts upon accommodation, and a 2 mm left pupil which was minimally reactive to light and constricts upon accommodation; (k) fundoscopic examination showed hazy media, vitreous



Cutaneous lesions on the tip of the nose; diffuse hair loss on the fronto-parietal area of the scalp; thinning of the eyebrows



Cutaneous lesions on the dorsal aspect of the hands, which were also present on the lower extremities



Multiple chancres on the glans penis and scrotum

Figure 2. Physical Examination Findings in the Patient

condensations, and exudates, with distinct disc border and attenuated vessels on both eyes. The rest of the neurologic physical examination upon admission were unremarkable (*Figure 2*).

Given the constellation of visual and dermatologic findings, an impression of panuveitis, both eyes, probably secondary to syphilis was considered. The diagnosis of syphilis was confirmed by a reactive serum Rapid Plasma Reagin (RPR) at 1:64 dilution, and a reactive serum Treponemal Enzyme Immunoassay (TP-EIA). HIV screening was also reactive, pending confirmatory results, with a CD4+ cell count of 15 cells/μL. Skin punch biopsy of the lesions on his hands, feet, and tip of the nose was also done.

Official histopathology results revealed lichenoid and interstitial dermatitis with which syphilis was highly considered (*Figure 3*). Cranial CT imaging showed mild

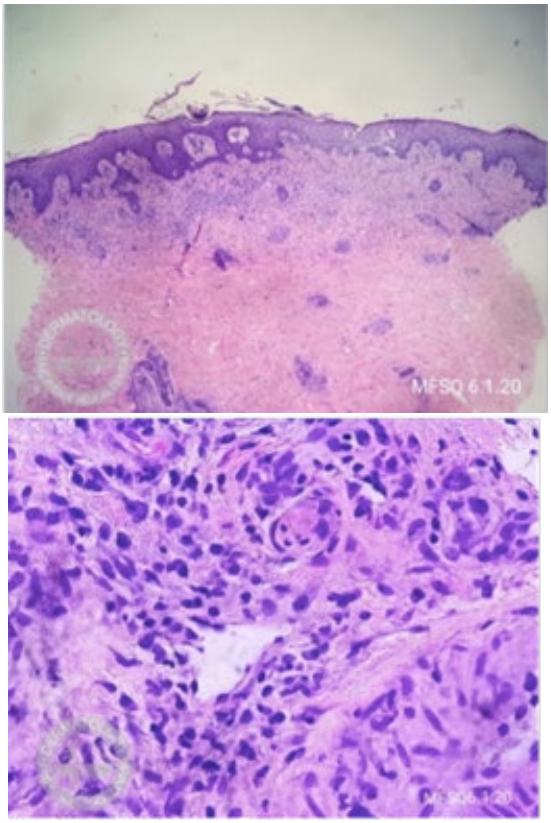


Figure 3. Skin punch biopsy showing lichenoid and interstitial dermatitis highly suggestive for syphilis (courtesy of the Department of Dermatology, East Avenue Medical Center)

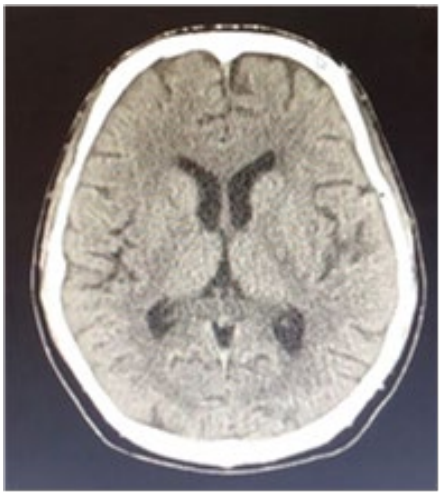


Figure 4. Cranial CT scan of the patient showing mild cerebral atrophy for a 34-year-old

cerebral atrophy (*Figure 4*). Lumbar tap was done, with an opening pressure of 14 cm H2O, revealed a colorless, clear cerebrospinal fluid (CSF), with lymphocytic pleocytosis, normal protein, decreased glucose, and a reactive CSF RPR. CSF meningitis/encephalitis panel including Gram stain, KOH, GeneXpert, and Cryptococcal Antigen Latex Agglutination System (CALAS) were unremarkable. A diagnostic challenge that was noted was the lack of availability of CSF VDRL test, hence, CSF RPR was used alternatively in this case. The history, physical examination, and diagnostic tests pointed to a diagnosis of neurosyphilis with ocular syphilis in an immunocompromised host. The patient was given intravenous penicillin G 3 million units every 4 hours for 14 days, together with ophthalmic medications (prednisolone, levofloxacin, and atropine ophthalmic drops). He was also started on antiretroviral therapy (ART). During the course of his admission, he was also diagnosed and managed with a number of opportunistic infections: *Pneumocystis* pneumonia, hospital acquired pneumonia, extrapulmonary tuberculosis, oral candidiasis, and onychomycosis. He was given the following medications: cotrimoxazole and prednisone for 21 days, ertapenem and levofloxacin for 14 days, Anti-Koch's regimen, and fluconazole. Prior to discharge, the patient was noted to have improved vision, and skin lesions were significantly improved. There were no noted adverse events with the treatment given. The patient was well-advised for close monitoring.

Upon follow-up, two weeks after discharge, repeat visual acuity testing showed significant improvement to 10/200 on the right eye and 20/125 on the left eye. Fundoscopic examination showed hazy media, optic nerve pallor, attenuated vessels and diffuse hypopigmented spots bilaterally. ART and ophthalmic medications were continued. Further improvement of the previously noted skin lesions was also documented.

Discussion

Multiple studies have shown that syphilis may impact HIV transmission and the course of HIV, and vice versa. Both ulcerative and non-ulcerative sexually transmitted diseases increase the risk of HIV transmission by approximately 3- to 5-fold. Wasserheit cited potential mechanisms for this epidemiologic synergy: there is increased recruitment of HIV-susceptible cells in genital tract inflammation, and disruption of epithelial barriers in the genital tract especially in ulcerative diseases, such as syphilis.[5] A study by Kofoed et al. showed that syphilis was associated with a decrease in CD4+ cell counts and an increase in HIV RNA levels that both improved after the treatment of syphilis, suggesting a possible impact of syphilis on the course of HIV.[9] On the other hand, HIV co-infection may have modified the natural history of syphilis by the following mechanisms: there is increased propensity of the disease to progress to neurosyphilis, a decreased latency period before the onset of neurosyphilis, and an increased severity of the manifestations.[6] The clinical presentation of syphilis with HIV co-infection may be atypical; having more persistent primary lesions, and is associated with an accelerated

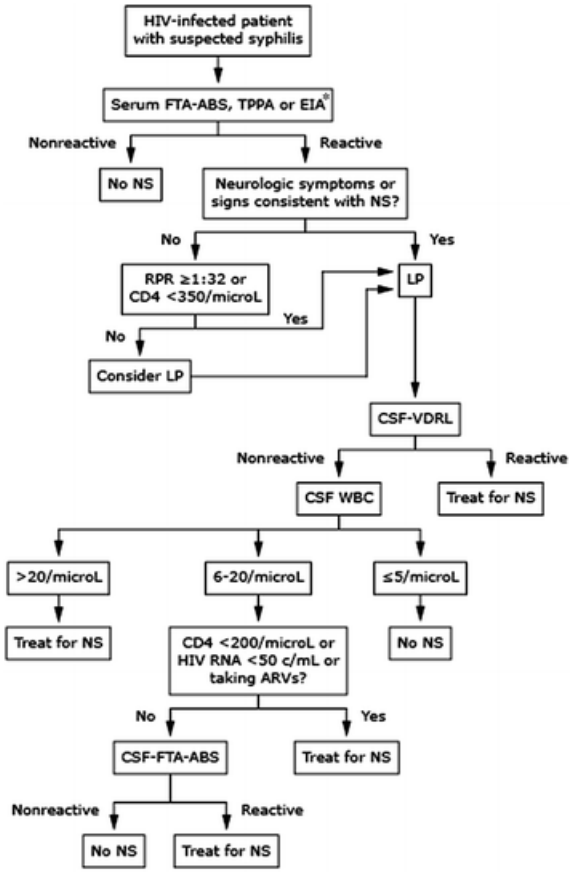


Figure 5. Algorithm for the diagnosis of neurosyphilis in an HIV-infected patient (Taken from: Morshed MG. Current trend on syphilis diagnosis: issues and challenges. Adv Exp Med Biol. 2014; 808:51-64.)

progression to tertiary syphilis.[5] A study by Rolfs et al. showed that HIV-infected patients with primary syphilis were more likely to have multiple chancres compared to the patients with primary syphilis but without HIV infection.[7] Hutchinson et al. also found that the clinical presentation of syphilis in patients with HIV infection present more often in the secondary stage and are more likely to have persistent chancres, signifying the overlapping of the stages.[8] Severe, persistent, and atypical cutaneous manifestations of syphilis tend to be more common in patients with HIV co-infection.[15] As also seen in our patient, alopecia is an uncommon clinical manifestation of secondary syphilis (2.9-7%); presenting as a "moth-eaten" patchy or diffuse, scalp alopecia associated with skin lesions of secondary syphilis.[16] These studies support the atypical clinical presentation of syphilis in our patient with newly diagnosed HIV infection.

With the emergence of the AIDS pandemic, neurosyphilis is now more often identified in young patients with HIV co-infection, and often presents early in the course of infection. Taylor et al. found that among patients with early syphilis, the incidence of neurosyphilis was 2.1% in those infected with HIV and 0.6% of those without HIV.[10] A retrospective study by Flood et al. found that the

median age for neurosyphilis was 39 years; 91% were male, and 64% were HIV-infected. Thirty-three percent presented with early symptomatic neurosyphilis and only 5% had late neurosyphilis.[3] A prospective study by Ghanem et al. involving HIV-infected patients with syphilis showed that 63% of cases presented with early neurosyphilis and that the median time to neurosyphilis diagnosis was 9 months.[4]

The diagnosis of neurosyphilis should be highly considered in an HIV-infected patient with the combination of a serum RPR of 1:32 or greater and a CD4+ cell count of 350 cells/μL or less.[11] The CDC and most experts recommend that CSF examination must be performed in HIV-infected individuals who are diagnosed with late latent syphilis, syphilis of unknown duration, those who present with neurologic, otologic, and ophthalmologic signs or symptoms, or suspected treatment failure.[6,17,18] Neurosyphilis is documented by a combination of a reactive serologic test, reactive CSF Venereal Disease Research Laboratory (VDRL) test, and abnormalities in CSF cell count and/or protein.[2] Involvement of the CNS in syphilis may be asymptomatic or symptomatic. Patients who lack neurologic signs and symptoms but have CSF abnormalities are classified as asymptomatic.[1] CSF VDRL is highly specific (100%) for neurosyphilis, but has low sensitivity.[19] A study done by Marra et al. showed that CSF RPR had lower sensitivity than the CSF VDRL (56.4% versus 71.8% for laboratory-diagnosed neurosyphilis, and 51.5% versus 66.7% for symptomatic neurosyphilis). Compared with the CSF VDRL, the CSF RPR has a higher false-negative rate.[20] However, some studies also show that CSF RPR could be an acceptable alternative to the CSF VDRL in the diagnosis of neurosyphilis.[21,22] The CSF RPR was done in our patient since CSF VDRL is not available. Aside from a reactive CSF VDRL, abnormalities in the CSF consistent with neurosyphilis include pleocytosis, often lymphocytic predominant, decreased glucose, and mild protein elevation.[23] Among persons with HIV infection, CSF leukocyte count usually is elevated (>5 white blood cell count [WBC]/mm^3).[2]

Cranial imaging serves as an adjunct to the diagnosis of neurosyphilis. Brightbill et al. found in their study among neurosyphilis patients that cerebral atrophy was the most common radiographic finding in neurosyphilis, observed in 37% of patients.[24] However, cerebral atrophy can also be found in patients with HIV-associated neurocognitive disorder (HAND).[26] This is consistent with the mild cerebral atrophy seen in our patient, although his neurologic examination was unremarkable except for the ophthalmologic findings. Other radiographic findings seen in neurosyphilis include cerebral infarction, leptomeningeal enhancement, white matter lesions, and cerebral gumma.[24] An algorithm for the diagnosis of neurosyphilis in an HIV-infected patient is shown in *Figure 5*.[25]

Symptomatic neurosyphilis include meningeal, meningovascular, and parenchymatous syphilis. Meningeal syphilis usually occurs less than a year after infection and may present with headache, nausea, vomiting, neck stiffness, cranial nerve involvement, seizures, and changes in sensorium. Meningovascular syphilis usually occurs up to 10 years after infection, and reflects meningitis associated with inflammatory vasculitis. Parenchymatous syphilis usually occurs 20-30 years after infection, and includes general paresis and tabes dorsalis. Manifestations of general paresis include changes in personality, sensorium, intellect and affect, hyperreactive reflexes, and Argyll Robertson pupils. Manifestations of tabes dorsalis include ataxia, foot drop, paresthesia, bladder disturbances, impotence, areflexia, loss of positional, deep pain, and temperature sensations, Argyll Robertson pupils, and optic atrophy.[1] Ocular involvement in syphilis is rare, and it usually occurs during the secondary and tertiary stages. It commonly presents with blurring of vision. Any structure of the eye may be affected, but uveitis (1-5%) is the most common presentation, and is frequently bilateral (67-89%).[13] Levy et al. (1989) also found that 85% of HIV-infected patients with ocular syphilis also had neurosyphilis, further strengthening the need for CSF examination in HIV-infected patients presenting with ophthalmologic signs and symptoms.[12] A higher frequency of posterior uveitis, posterior placoid chorioretinitis, necrotizing retinitis and optic nerve involvement were noted among HIV co-infected patients and that they have a more severe course and may relapse despite high-dose intravenous penicillin therapy.[14]

Patients with neurosyphilis and ocular syphilis are given aqueous penicillin G 18-24 million units per day for 10-14 days. Multiple studies have documented the treatment response in ocular syphilis with penicillin treatment. Shalaby et al. noted in their study among patients with ocular syphilis with HIV co-infection that with intravenous penicillin treatment, 67% of patients had improved vision, and 92% had reduced ocular inflammation.[29] Tsuboi et al. also noted that the best-corrected visual acuity improved in 89% of patients, and 15% developed recurrence after treatment.[28] In this case, the ophthalmologic findings were consistent with panuveitis; with significant improvement in visual acuity after treatment with penicillin. Patients with HIV co-infection are managed with the same regimen as those without HIV.[2] However, HIV co-infection was found to contribute to increased rates of treatment failure of syphilis.[5] Ghanem et al. found that a CD4+ cell count of less than 200 cells/μL at the time of syphilis diagnosis was associated with an increased risk of serologic failure.[27] Hence, the CDC recommends that nontreponemal titers be repeated more frequently at 3-6 months in HIV co-infected patients and that CSF examination be repeated at six month-intervals. The receipt of ART was associated with a 60% reduction in the rate of serologic failure.[27]

Conclusion

Through this case, it was elaborated that with HIV co-infection, syphilis may present atypically—with multiple, persistent, primary lesions; with overlapping of the stages, and increased frequency of neurosyphilis presenting early into the infection. Because of the increased incidence of neurosyphilis in HIV patients, CSF

examination for syphilis is recommended in those with neurologic, (including ophthalmologic) signs and symptoms. Likewise, in patients presenting with neurosyphilis, HIV testing is also recommended.

Although *Treponema pallidum* sub-species *pallidum* has remained susceptible to penicillin, HIV co-infection contributes to the increased rate of treatment failure. Frequent monitoring for treatment response should be done. Administration of antiretroviral therapy is also recommended in patients with syphilis and HIV co-infection as it is associated with a decreased rate of serologic failure.

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