SYPHILIS AND HUMAN IMMUNODEFICIENCY VIRUS CO-INFECTION

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Co-infection of syphilis and AIDS has profound implications for the African American community. The purpose of this review is to: evaluate the historical background of HIV and syphilis and their similarities in pathogenesis; review the epidemiology of syphilis and HIV co-infection, and implications for continued prevention efforts; examine the effect of syphilis on HIV transmission and acquisition; and, to examine the effects of HIV infection on syphilis transmission, diagnostic and serologic changes, clinical course, and treatment.

The prevalence of HIV is higher in those with syphilis; moreover, the prevalence of HIV and syphilis co-infection is highest in African Americans. There may be humoral and cellular immune similarities. HIV may affect the transmission of syphilis, alter its serologic diagnosis, and accelerate and change the clinical course and response to treatment. In conclusion, combined infection of HIV and syphilis may alter the clinical presentation and course of either disease. There are historical and immunologic similarities and the high prevalence in African Americans compared to other groups is of great importance for prevention efforts. (*J Natl Med Assoc.* 2003;95:363-382.)

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"Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you."

—Sir William Osler, 1897

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BACKGROUND

Syphilis

The history of syphilis dates back to antiquity. In Europe, syphilis was epidemic in the late 15th century and its manifestations were quite severe—it was called the "great pox," "lues venereum," and "morbus gallicu."[1] The disease takes its name from the title of a poem written in 1530 by Girolamo Fracastoro titled *Syphilis Sive Morbus Gallicus,* which means "Syphilis or the French Disease."[2]

Spirochaetes, coiled and twisted organisms were described in 1876 by Weil. The name treponemes was coined by the German bacteriologist, Fritz R. Schaudinn in 1905.[3] Philip Ricord (1799-1889) was the first person to show that syphilis

and gonorrhea were two separate diseases. Ricord showed by a series of experiments involving 2500 inoculations that gonorrheal pus could not cause syphilis.[1,4] The etiology of syphilis was discovered in 1905 by Schaudinn and Hoffmann when they visualized spirochetal organisms in early infectious lesions.[1]

In 1906, Wassermann introduced the first serological test for syphilis to become known as the Wassermann test.[1,4] During the late 19th century, most of the clinical manifestations of syphilis were known, but the fate of the individual with untreated disease was not. It was not known for certain whether or not the treatment for syphilis was effective, or if remissions and relapses were simply a natural part of the disease process. Boeck designed a study to resolve this issue.[5]

Between 1890 and 1910, Boeck hospitalized 2000 patients with primary and secondary syphilis until the lesions healed without treatment. These lesions were carefully described on admission to the hospital, and their regression and time of disappearance was carefully recorded.[5] A weakness of the study by Boeck was that it did not involve serology or darkfield microscopy, which were unavailable in Oslo before 1910.[6]

In 1925, Bruusgaard began a retrospective study of the work of Boeck. Bruusgaard studied 473 of Boeck's original patients, of which 309 were living and 164 were dead.[6] Most of the patients had spontaneous cures (27%) and only 0.8% of patients died of syphilis. Neurosyphilis was seen in 9.5% and latent syphilis was seen in 14.1%. In 1948, a re-examination of the work of Boeck was done by Gjestland. He found that 25% of untreated syphilitics relapsed, and that this was the natural history or course of untreated disease. These studies by Gjestland of Boeck's work form the basis of what we know about the natural course of untreated syphilis. It is commonly called the "Oslo study."[5,6]

Despite the existence of the study by Boeck, the United States Public Health Service (USPHS) in 1932 undertook a prospective study involving black men from Macon County, Alabama, with untreated syphilis observed to autopsy.[7,8] Dr. Donald H. Rockwell of the USPHS (R) summarized the results in 1964 during a symposium marking the 30th anniversary of the Tuskegee Syphilis Study. In Macon County in 1932, a total of 26% of the male population tested who were 25 years of age or older were positive by two tests for syphilis. The original study group was composed of 412 of these men, who had received no treatment, and who had historical and laboratory evidence of syphilis. A total of 204 men of comparable age without syphilis served as the control group.

Mortality records, during the first 12 years of observation, revealed that 25% of the syphilitics and 14% of the controls of comparable ages had died. It was calculated that at age 25, untreated male syphilitics would have a reduction in life expectancy of approximately 20%. By 1952, after 20 years of follow-up, 40% of the syphilitics and 27% of the controls had died; at that time, the life expectancy of individuals from ages 25 to 50 with syphilis was determined to be reduced by 17%. The primary cause of death in 30% of the infected group was attributed to syphilitic involvement of the cardiovascular or central nervous system. As of Dec. 1, 1963, of the original 412 syphilitics, 242 were known to be dead.[7] In the 1940's, when penicillin was shown to dramatically and effectively treat syphilis, the USPHS continued the study.[9,10] In a White House ceremony on May 16, 1997, President Bill Clinton apologized for the Tuskegee Syphilis Study.[11]

HIV

It is not possible to say when or how acquired immunodeficiency syndrome (AIDS) started. Theories on this subject abound; nevertheless, the onset of AIDS in the United States dates back to the late seventies.[12,13] The sporadic occurrence of Kaposi's sarcoma in homosexuals was recognized as an unusual problem in the spring of 1981.[14,15] Clinicians and epidemiologists in New York, San Francisco, and Los Angeles reported on clusters of unusual diseases predominantly in

homosexual males.[16-19] Diarrhea, in homosexual men, was sometimes disputedly called the "gay bowel syndrome."[20-22]

In June and July of 1981, published reports appeared in *Morbidity and Mortality Weekly* on 25 patients with Kaposi's sarcoma and 15 patients with Pneumocystis pneumonia in previously healthy homosexual males, some of whom were diagnosed with these illnesses since 1979.[14,17] Following publications of the initial reports, there were additional cases reported to the Centers for Disease Control (CDC) and what was striking was that all of these patients showed a marked depression of thymus dependent lymphocytes and of *in vitro* proliferative responses to mitogens and antigens.[18] In 1981, this syndrome of immunodeficieny was called "gay-related immune deficiency (GRID).[23,24] In 1982, the term "acquired immune deficiency syndrome" (AIDS) replaced the term GRID.[24] Surveillance for AIDS began in 1981 and in 1983 the cause of the disease was controversially discovered. In the United States, it was called HTLV-III (human T-lymphotrophic virus) and in France LAV (lymphadenopathy virus). In 1986, the virus was named human immunodeficiency virus (HIV).[24,25]

EPIDEMIOLOGY OF SYPHILIS AND HIV CO-INFECTION

In 1998, Congress initiated funding for the syphilis elimination effort.[26] In 1999, the US Surgeon General developed and announced the "National Plan to Eliminate Syphilis from the United States." This was in response to several factors, which included the important role of syphilis in facilitating the transmission of HIV infection, and the disproportionate impact of syphilis on racial and ethnic minorities.[27-29]

The rates of syphilis over the past 10 years has been declining. In 1990, there were 50,578 reported cases of primary and secondary (P&S) syphilis. In the year 2000 the number of reported cases had fallen to 5979. This represented the fewest number of cases ever reported in the US and lent hope that syphilis could be eliminated from the US; however, the rate of decline has slowed from the peak decline of 20% per year since the last major syphilis epidemic peaked in 1990 to the 9.6% decline from 1999 to 2000.[29] The rates in blacks have declined less than that of whites, and the incidence in blacks in 1999 was 30 times that of whites.[26,27,30] In 2000, the rates of syphilis were 21 times higher in blacks, with African Americans representing 70.8% of all the cases of primary and secondary syphilis.[31]

Syphilis is reported primarily in only specific areas of the country. In the year 2000, 2520 (80.2%) of the 3130 counties in the US reported no cases of P&S syphilis. Half of all P&S syphilis cases were reported from only 21 counties. Five hundred and ninety-five counties accounted for more than 99.5% of all reported P&S syphilis cases (5952 out of 5979). Almost 70% of these counties are located in the southern part of the US.[29] The syphilis rate for African Americans was almost 60 times greater than for non-Hispanic whites during the 1990s.[31] This may represent a reporting bias, since many African Americans may utilize public clinics more than whites, and the reporting may be more complete from these clinics; nevertheless, it is still of great concern. Primary syphilis among African Americans in LA County is 20 times more prevalent than among whites and three times more common among Latinos than whites.[32]

There are no large-scale studies on the prevalence of syphilis and HIV co-infection or patients with syphilis and AIDS in the US. There are many smaller studies, several of which are from Africa or Asia, which try to gauge the prevalence of syphilis and AIDS.[33-38]

A serosurvey of syphilis and HIV in Nigeria by Dada et al. found that the prevalence of syphilis was extremely low. Four percent of female sex workers (FSW) in Lagos were positive by Rapid Plasma Reagin (RPR) test or Treponema Pallidum Hemagglutination Assay (TPHA). By contrast, 60% of FSW age 20 to 29 were HIV-1 positive, and 14% age 30 to 39 were HIV positive. The low incidence of syphilis is a widely observed phenomenon in West Africa and contrasts with the sit-

uation in East, Central, and Southern Africa where syphilis appears to have a higher prevalence.[33]

In Harare, Zimbabwe, Gwanzura et al. examined 709 sera from 580 men. There were 78 cases of active syphilis in the cohort, giving a prevalence of 2.3%. The prevalence of HIV in the cohort was 19.8%. There was a strong association between syphilis, whether active or historic, and HIV seropositivity. Men who were HIV positive had a three-fold higher risk of having serological evidence of active syphilis.[34]

In the US, surveillance data is available for syphilis and AIDS separately, but not together. It is implied that counties such as those located in the southeast or south Atlantic region should have an increasing incidence of AIDS since most new cases of syphilis appear in the southeastern United States.[39] Indeed, some of the highest incidence of HIV occur in the southeast, and it has been a growing area for HIV incidence.[29,39] While the sustained spread of syphilis has not been reported in the US in recent years, periodic outbreaks of the infection, as well as localized high prevalence areas, remain an important public health problem.[32]

Many metropolitan urban areas continue to experience increasing numbers of syphilis cases, and dramatic disparities still exist among some populations. Nuttbrock studied 184 attendees in a New York City soup kitchen for the prevalence of HIV and syphilis. He detected HIV antibodies in 18% of the clients with high levels of exposure to syphilis (12%).[40] Blocker systematically reviewed the literature of US studies with HIV seroprevalence data in patients with syphilis. Thirty studies were identified and analyzed. The median HIV seroprevalence in men and women infected with syphilis was 15.7%. Seroprevalence in men was 27.5%, and in women 12.5%. Seroprevalence in men who have sex with men (MSM) ranged from 64.3 to 90.%, and in intravenous drug abusers (IVDU) from 22.5% to 70.6%.[41]

One of the largest studies done in the US to analyze the prevalence of syphilis in patients who were HIV positive was actually designed to determine if syphilis could be a marker for HIV infection during the window period where HIV serologic tests may be negative. This study, conducted by Herrera et al., appeared in *Transfusion* in 1997. Herrera analyzed demographic and laboratory information on blood donations made between January 1992 and June 1994 in 18 American Red Cross regions. Of 4,468,570 donations, 12,145 (0.27%) were STS (serologic test for syphilis) positive and 377 (0.008%) were HIV positive. Among donations that were negative on other screening tests, STS-reactive donations were 12 times more likely to be HIV positive.[42]

Harkess examined the interaction between syphilis and HIV in Oklahoma. They conducted an unlinked HIV seroprevalence survey using serum specimens submitted to the Okalahoma State Department of Health for serologic testing for syphilis. Of 2426 excess serum specimens tested for syphilis, 2412 (99.4%) were fully tested for HIV-1 antibodies. A total of 979 (41%) tested positive for syphilis and 73 (3%) were HIV positive. Persons whose serologic test results were positive for syphilis were 8.3 times more likely to be HIV-1 seropositive than those whose test results were nonreactive for syphilis.[43]

In a study on HIV prevalence and associated syphilis among injecting drug users in LA County between 1994 and 1996, Lopez-Zetina et al. recruited 513 African American and Latino IDUs who were then screened for syphilis and HIV antibodies. Of the sample, 74% were male; 70% were African American; 30% Latino; and the median age was 43. Serological prevalence of HIV was 2.5% and of syphilis 5.7%. None of the participants were co-infected for HIV and syphilis at baseline or at any of the six-month follow ups. African Americans were more likely to be syphilis incident cases when compared with Latinos. This study showed an apparent paradox of low HIV prevalence and rare HIV seroconversion and high syphilis incidence among IDUs in Los Angeles. But in Los Angeles, a small percentage of the sample reported injecting in shooting galleries in the past six months, as opposed to IDUs in other parts of the country.[32]

The increased prevalence of syphilis in patients

with HIV infection could represent increases in sexually risky behavior, in addition to the increased transmission of HIV in patients with syphilis.[44] In Atlanta, Kalichman recruited 223 men, 112 women and five transsexuals who were HIV-positive to complete a confidential self-reported survey involving sexually-transmitted infections (STI) or symptoms and sexual practices. Seventy-eight percent (78%) of participants had been sexually active in the previous three months. Thirty-six percent reported engaging in unprotected intercourse in the previous three months despite being HIV-positive. For the entire sample, 42 (12%) of the participants reported a STI in the previous three months and 40 (11%) experienced symptoms of an STI. Of the 42 (12%) who reported having an STI in the previous three months, six of 24 men (25%) and four of 18 women (22%) reported having syphilis. This study was based on a self-reported survey and did not involve laboratory evaluation for syphilis seroprevalence. Because of reporting biases and the lack of serologic tests for syphilis, the survey may actually underreport the true prevalence of syphilis in this group.[45]

The epidemiological and clinical problems of HIV and syphilis have important implications for the prevention and clinical management of co-infection.[32] According to Kalichman, there is a need for HIV prevention interventions targeted to people who are already known to be infected with HIV. Interventions that focus on reducing substance use, reinforcing consistent condom use, and enhancing motivation to practice safer sex, should be targeted to sexually active people with HIV. Interventions for people already infected but continuing risky sexual practices may prove more efficient and cost-effective than interventions that target masses of uninfected people.[45]

HIV AND SYPHILIS SIMILARITIES

These two diseases (AIDS and syphilis) have much in common and they have synergistic negative effects on the host which have serious clinical implications.[5] It is well known that HIV leads to loss of CD4+ cells with multiple consequences, but it is not generally recognized or appreciated that syphilis also has an effect on both cellular and humoral immunity early on in the disease, which may or may not be transient.[47-50] Positive skin tests are rare in primary or secondary syphilis. Patients with primary or secondary syphilis have impaired lymphocytic responses to phytohemagglutinin (PHA). Plasma from patients with secondary syphilis causes reduced levels of blastogenesis of normal lymphocytes. Concanavalin A (Con A) and PHA induced proliferation of purified T-cells are markedly reduced during early infection, while the response to classical B-cell mitogens is normal. This early decrease in cellular immunity in early syphilis may account for some of the widespread dissemination.[50]

There are humoral immune responses in both HIV and syphilis.[50-53] The humoral responses to syphilis involve two types of antibodies. The first class of antibodies is directed toward the cardiolipin component of the treponeme. The humoral responses towards cardiolipin form the basis of the non-treponemal tests for syphilis (what is commonly called the Serologic Tests for Syphilis [STS]). These include the Venereal Disease Research Laboratories test (VDRL) or the Rapid Plasma Reagin test (RPR).[54] The cardiolipin component composes approximately 10% of the organism and also is found in mammalian cells. It is not clear whether anticardiolipin is directed toward the spirochete or directed toward mammalian tissue altered by the spirochete.[50,54,55] The other class of antibodies is targeted against the Treponeme directly and they are measured by the fluorescent treponemal antibody absorption (FTA-ABS) test, the microhemagglutination Treponema pallidum (MHA-TP) test, or the Treponema pallidum immobilization (TPI) test.[1,54,55]

HIV may cause a polyclonal expansion of immunoglobulins (Ig) which could lead to diagnostic confusion in considering the diagnosis of syphilis in an HIV infected patient.[56] This polyclonal expansion of Ig may be the result of B-cell activation secondary to a decreased effect of CD8 suppression. This may lead to the unregulated pro-

duction of immunoglobulins, and this is a well-known complication of HIV infection.[53]

The B-lymphocytes are present in normal numbers, but show increased spontaneous Ig production and are refractory *in vitro* and *in vivo* to further stimulate B-cell mitogens and neo-anti-production of antibodies directed against previously encountered antigens.[56] The B-cell may also be depressed, and if so, the response of the B-cell to new mitogens with Ig also may be depressed.[56,57] It is conceivable that the macrophage, which is an antigen processing cell and which is a primary target of the HIV virus, may fail to adequately present processed antigens to B-cells, thereby leading to a depressed humoral immune response. On the other hand, a depression of B-cell function and consequent decreased humoral response may be secondary to a lack of helper-effect of the CD4 lymphocyte on the B-lymphocyte.[58]

We are presented then with two possible scenarios of infection with HIV on the humoral response: 1) polyclonal B-cell activation with increased levels of immunoglobulins or, 2) lack of B-cell activation with a decreased response to mitogens or antigens. If you have polyclonal expansion of Ig, then the STS may remain positive after eradication of the organism. The expected decrease in STS titers may take longer to occur. A patient adequately treated previously could conceivably present with serology suggestive of recent infection or reinfection. On the other hand, depressed B-cell functions may lead to a false negative serological test.[55,59-61] Clinically, patients with concurrent HIV and syphilis infections or with a history of syphilis in the past with a positive HIV test may present either with false negative serologies or they may present with false positive serologies after adequate treatment. There are other causes of negative serologies to consider, for example, in early primary syphilis, the STS may be negative. In secondary syphilis, the prozone phenomenon may occur in which undiluted specimen has so many antigens that antibodies are not detected until the specimen is diluted.[61]

The mechanism and cause of syphilis dissemination in the host is largely unknown.[62] As we have previously shown, syphilis may cause transient depression of cellular immunity; nevertheless, there are ample areas of effector immune responses to the spirochete involving polymorphonuclear neutrophils (PMN's) and humoral mechanisms. Why, in spite of these responses, T. pallidum disseminates even in the immunocompetent hosts, is unknown and similar in some regards to the spread of the HIV in the host organism.[47, 62]

In the primary stage of syphilis, the body brings to bear numerous defenses. Afterwards, there is attenuation or resolution of the primary chancre, but instead of resolution of the disease, it may go, if untreated, to a secondary stage in which the person has widespread dissemination and symptoms and signs ranging from malaise to prostration and cachexia. There may be headaches, low grade fever, asymptomatic meningitis (8-40%), painless adenopathy (70-75%), jaundice (up to 12%) and, though rarely, arthritis and rapidly progressive glomerulonephritis.[1] The skin lesions may actually represent modified ulcers, which appear the way they do because of immune modulation. Rabbits inoculated with spirochetes intravenously, form generalized ulcers instead of the papular rash of syphilis. It is conceivable that patients who are severely immunocompromised may manifest these generalized ulcerated lesions especially if attained through transfusion.[1,63]

After the secondary stage of syphilis, there is a latent period when infection is not manifest. Treponemes are still present and viable but are hidden in different organs, such as the brain and heart. Later, without treatment, 26% of patients have a relapse typically involving the central nervous system (CNS) or the cardiovascular system (CVS). This represents a tertiary stage of syphilis infection and could happen from one to 20 years after the primary infection. The pathogenesis of this and how the organism remains viable and quiescent for up to 20 years is unknown. This is similar to the so called quiescent state of HIV infection.[6,60] It is recognized that this "quiescent" state of HIV is clinical and not virological and that the

virus is continuously replicating.[64-66]

It is easy to see that we have two organisms (HIV and T. pallidum) that have profound effects on the immune system and are both able to hide out, so to speak, for years, without clinical manifestations. Could it be then that they can possibly work synergistically to the detriment of the host? In 1989, Hook asked several important questions concerning the relation of HIV and syphilis co-infection.[56] Some of these questions will be revisited and include:

1. Does syphilis facilitate the transmission or the acquisition of HIV?
2. Does HIV alter and/or accelerate the clinical manifestations of syphilis?
3. Does HIV alter the diagnostic detection of syphilis?
4. Does HIV affect the treatment response to syphilis?

DOES SYPHILIS FACILITATE THE TRANSMISSION OR THE ACQUISITION OF HIV?

There is strong epidemiological evidence suggesting that a history of past syphilis increases the risk of AIDS. Studies in Kenya and Zaire have reportedly demonstrated an association between reactive serological tests for syphilis and a history of genital ulceration and the likelihood of HIV infection.[56,67] In North America, syphilis or a positive serological test for syphilis (STS) is associated with an increased risk of seroconversion for HIV. Previous herpes infection also was associated with an increased risk of seroconversion.[56] Herpes has been shown to increase the shedding of HIV in coinfected individuals.[41] The relation between STDs and genital HIV shedding is potentially confounded by the level of immunosuppression. Advancing immunosuppression may promote STD acquisition or persistence, as well as HIV shedding.[68]

According to Fleming, recent scientific evidence supporting a role for STDs in facilitating HIV transmission has come from three types of studies: 1) Biological plausibility suggests potential mechanisms at the biological level; 2) Cohort studies of HIV seroconversion estimate the increase in risk of HIV infection associated with specific sexually transmitted diseases (STDs) or STD syndromes; and, 3) Community level intervention studies have begun to quantify the effect that STD treatment can have on HIV incidence.[69]

Biologic Plausibility

Both primary syphilis and other ulcerative genital lesions that increase the risk of HIV infection, disrupt the epithelial or mucosal surfaces, which provides a portal of entry for the virus to enter the systemic circulation.[56,67,70] This may explain why anal, and other traumatic, sexual practices may enhance HIV acquisition. Genital ulcers bleed frequently during sexual intercourse, which results in potential increases in HIV infectivity.[68] Disruption of the genital mucosa is associated with the recruitment of inflammatory cells such as CD4+T lymphocytes and macrophages. The presence of these cells can facilitate transmission of HIV virions from HIV-infected persons to uninfected persons or provide additional targets for HIV entry in HIV-negative persons who are being exposed to the virus. It should be noted that HIV has been isolated from genital ulcer exudates.[41,63,68] The classic chancre of primary syphilis is a painless, single, indurated ulcer with a clean base.[1] The base of the chancre contains T-lymphocytes and macrophages—the primary targets of HIV. They are present in an ulcerated area that can readily be exposed to blood and body fluids.[41,56] The painless nature of the chancre may allow some patients to continue having sex, thereby increasing the risk of transmission and acquisition of HIV infection.

Several lines of evidence suggest that mucosal dendritic cells that express both CCR5 and CD4 receptors are targets for HIV-1. People who are homozygous for a deletion (delta 32) in the CCR5 receptor may have at least partial resistance to HIV-1 infection. Infected dendritic cells transport HIV-1 to lymph nodes, where the infection of CD4 cells so characteristic of HIV disease occurs. In addition, there is evidence that infected dendritic

cells may transmit HIV to blood and tissue lymphocytes.[71-73] Classic STDs, such as syphilis, could facilitate HIV-1 transmission by increasing either the infectiousness of the index case, the susceptibility of the partner or both.[71] Macrophage-tropic (M-tropic) strains of HIV-1 are some of the most infectious and the most common phenotype transmitted sexually. M-tropic strains use CCR5 as a key co-receptor for the virus. M-tropic strains replicate within macrophages and not within established CD4 cell lines, whereas T cell-tropic strains of HIV-1 use the chemokine co-receptor, CXCR4 and are generally unable to infect macrophages, but replicate in CD4 T cell lines.

Sellati showed that treponemal lipoproteins increase expression of CCR5 and decrease expression of CXCR4. He concluded that the differential expression of CCR5 and CXCR4 in the genital ulcer macrophages and CD4 T cells favors the transmission of M-tropic strains of HIV-1 and may explain why patients with syphilis acquire HIV so readily.[74]

Treponema pallidum lipoproteins have been shown to increase HIV-1 replication.[71] These lipoproteins induce HIV-1 gene expression in human monocytic cells via NF-KB dependent mechanisms.[74] T. pallidum also may disrupt mucosal tissues, increase the number of cells receptive to HIV-1, or increase the number of receptors expressed per cell. Patients with genital ulcers also have increased excretion of HIV-1 RNA in semen, which may result from local concentrations of cytokines or because patients have a more advanced stage of the disease. Cervicovaginal ulcers may be associated with increases in HIV-1 in lavage samples, which decrease after treatment of the STD.[71]

Epidemiologic Evidence

As previously noted, Blocker systematically reviewed 36 US studies to assess HIV infection in patients with syphilis. The median HIV seroprevalence was 15.7%, with men having a prevalence of 27.5% and women 12.5%. He concluded that co-infection with syphilis increases the risk of transmitting HIV and that there is a high rate of co-infection in the US.[40] Greenbalt in a study involving 1115 heterosexual men with genital ulcers in an STD clinic in Nairobi, Kenya, found a seroprevalence of HIV of 16.5%. The prevalence of HIV was increased in men with a past history of genital ulcers.[75] Each of the major genital ulcer diseases—herpes, syphilis and chancroid have been associated with an increased risk of acquiring and transmitting HIV. STDs may increase the overall risk of acquiring HIV from three to five times.[63,76] In general, STDs seem to have a stronger effect on the susceptibility of acquiring HIV as opposed to the transmission of HIV.[76]

Dickerson examined the role of genital ulcer disease (GUD) as a risk factor for transmission of HIV by reviewing 27 epidemiological studies, which were case-controlled, cross-sectional and cohort studies. Approximately two-thirds of the analyses reported a statistically significant association between GUD and HIV. GUDs included syphilis, chancroid and herpes. Nine of 10 case-controlled studies showed a statistically significant association between syphilis and HIV.[68]

Fleming reviewed scientific studies on STDs' role in the sexual transmission of HIV infection.[69] There was strong evidence showing that both ulcerative and non-ulcerative STDs promote HIV transmission by augmenting HIV infectiousness and HIV susceptibility via a variety of biological mechanisms. Four of six studies with 10 or more syphilis cases revealed a significant association between syphilis and increased risk of HIV transmission on multivariate analysis, with risk estimates that ranged from 2.3 to 8.6. Strong evidence indicating that syphilis facilitates HIV transmission also was provided by a study of more than 5100 patients who were tested twice for HIV at four Miami STD clinics. Patients who were diagnosed with syphilis, between the two HIV tests, were almost three times as likely to HIV seroconvert, as those who were diagnosed with syphilis before the first HIV test. These patients, in turn, were almost one and a half times as likely to seroconvert as those in whom syphilis was never diagnosed.

Interventional Studies

Intervention trials have established the importance of STDs in HIV-1 transmission. The interventional trial by Grosskurth et al. in Mwanza, Tanzania, involved 12,537 individuals with a baseline HIV. They had intervention and non-intervention arms. HIV incidence over two years was 48 of 4149 in the intervention communities, and 82 of 4400 in the comparison communities. HIV incidence was consistently lower in the intervention communities. They concluded that improved STD treatment reduced HIV incidence by about 40% in this rural population of Mwanza, Tanzania.[77] A causal link between HIV-1 and classic STDs has been demonstrated. In countries where STDS and HIV-1 coincide, treatment of STDs can be expected to reduce transmission of HIV-1 in a cost-effective manner.[71,77]

The Rakai trial in Uganda also tested the hypothesis that community-level control of sexually transmitted disease would result in lower incidence of HIV-1 infection in comparison with control communities; however, they observed no effect of the STD intervention on the incidence of HIV-1 infection and concluded that a substantial proportion of HIV-1 acquisition appears to occur independently of treatable STD co-factors. Some explanations for the differing results between the Mwanza and Rakai trials include: 1) The most important difference between the two study population was HIV-1 exposure, with prevalence in Rakai being 15.9 and in Mwanza 4.1%.[78] 2) There were potential differences in the prevalence of incurable STDs (such as genital herpes); the greater importance of symptomatic rather than asymptomatic STDs for HIV-1 transmission; and possibly greater effectiveness of continuously available services than of intermittent mass treatment to control rapid STD reinfection. The effect of treating STDs are more important in areas with higher rates of treatable STDs and where HIV prevalence is not at a very high level in the general population.[79] Periodic mass treatment of STDs as occurred in the Rakai trial may not be an effective method for STD control because it is intermittent.[80]

Intervention studies currently suggest that intermittent mass treatment alone delivered to the general population is not an effective approach to STD control for HIV prevention, particularly in a late HIV epidemic with relatively low rates of curable STDs. Targeted mass treatment among high frequency transmitters or others with high STD incidence or prevalence at relatively short intervals deserves additional examination in combination with establishment of high quality, continuous STD treatment services to achieve a rapid initial reduction in STD rates.[69] It should be noted that neither the Mwanza or Rakai trials were syphilis specific.[77,78]

In summary, chancres and ulcerative lesions: 1) increase the acquisition of HIV by providing target cells for potential infection (macrophages and lymphocytes); and 2) increase the transmission of HIV by facilitating transfer of cell-rich fluid or blood.

DOES HIV ALTER AND/OR ACCELERATE THE CLINICAL MANIFESTATIONS OF SYPHILIS?

The clinical presentation of syphilis in HIV-positive patients is commonly the same as in HIV negative patients; however, unusual and atypical features may be seen. Accelerated progression through the syphilitic stages may occur. This progression may be related to the level of immunosuppresion.[63] The primary stage of syphilis may consist of multiple or more extensive chancres in the HIV patient.[63,81] HIV patients with syphilis are more likely to present with secondary syphilis and those with secondary syphilis are more likely to have persistent chancres.[59] Syphilis is known as the "great imitator." The signs and symptoms of secondary syphilis include fever, malaise, diffuse lymphadenopathy, headache and weight loss—all common findings in HIV infected patients with or without opportunistic infections. The altered immune responses of HIV infected patients may lead to atypical clinical presentations of secondary syphilis.[60] For example, Langtry reported on a case of a 68-year-old man who had secondary syphilis and was treated with prednisone for six months for an alleged allergic drug reaction. He eventually developed a positive VDRL and was found to be HIV positive.[82]

Patients with HIV infection who acquire syphilis may be more likely to progress to clinical neurosyphilis than those without HIV infection.[56] Johns et al. reported on four cases of neurosyphilis occurring within 18 months in HIV-positive men. Meningovascular syphilis developed in one patient within four months after a primary infection in a manner consistent with an accelerated course of syphilitic infection. HIV infection may alter the natural course of syphilis because of the profound defects in cell-mediated immunity. In patients with early syphilis and HIV infection, a synergistic immunodeficiency state may be due to a transient treponemal induced immunosuppresion. Alternatively, meningeal inflammation induced by either pathogen could allow the other agent to penetrate further into the CNS.[57]

DOES HIV ALTER THE DIAGNOSTIC DETECTION OF SYPHILIS?

In 1964, Spangler et al. described 24 patients with negative serologies and syphilis. Of these, 16 were thought to be due to the prozone phenomenon.[61] According to Spangler, a survey by Huriez of 617 cases of late visceral syphilis diagnosed from 1947 to 1967 found that 5% of aortic and general paresis and 3% of ocular syphilis were seronegative diagnosed by TPI. We see that even before the onset of AIDS, there had been questions about syphilis and negative serologies.

Reagin and treponemal antibody tests are highly reliable in diagnosing secondary syphilis. However, patients infected with HIV may respond abnormally to antigenic stimulation and may fail to develop typical serologic responses to infections.[60] False-negative serologic tests for syphilis do occur in immunodeficient HIV-infected persons with clinically evident syphilis and early in the course of congenital syphilis.[81] Most HIV-infected patients appear to have a normal serologic response to T. pallidum infection, however, some patients with biopsy-confirmed secondary syphilis have had negative nontreponemal and treponemal tests for syphilis. Biological false-positive (BFP) STS occur more frequently in HIV-positive patients.[83,84] This may be due in part to some patients having unusually high titers on nontreponemal tests possibly because of HIV-related polyclonal B-cell stimulation.[85] False negative treponemal and nontreponemal tests occur somewhat more frequently in patients who have HIV infection. If suspicious lesions are present in a patient with HIV infection, but serologic tests are negative, biopsy of the lesions should be performed for microscopic examination to identify spirochetes.[86] In patients with ulcerative lesions, the polymerase chain reaction (PCR) may detect more cases of syphilis than darkfield examination or RPR.[87] Patients with HIV infection who are severely immunocompromised may have a negative serologic test because of the inability to mount an antibody response to T. pallidum.[54]

Hicks et al. reported on a case of an HIV-infected man with Kaposi's sarcoma and secondary syphilis whose VDRL and FTA were repeatedly nonreactive. Correct diagnosis required biopsy of a skin lesion with silver staining to show spirochetes. Clinicians treating HIV-infected patients should be aware of the problems of serologic diagnosis of syphilis in these patients. Biopsy samples of appropriate tissues staining for spirochetes may be needed to arrive at the correct diagnosis.[60] When clinical findings suggest syphilis but serologic tests are negative, then a darkfield examination should be done, which readily diagnoses syphilitic cutaneous or genital lesions.[85,88]

Augenbraun in a study involving 525 patients found that HIV serostatus is not associated with a lack of reactivity of Treponemal specific tests (TST) which are the FTA-ABS and MHA-TP. TSTs did not invariably remain reactive. They could demonstrate no association between the loss of TST reactivity with HIV serostatus. The prevalent belief that the TST is invariably reactive from the time of infection for the life of the patient was not supported by the data. HIV serostatus was not associated with a lack of TST reactivity in untreated early stage syphilis, substantiating the utility of TST as confirmatory tests for clinically evident syphilis in HIV seropositive individuals.[89]

DOES HIV AFFECT THE TREATMENT RESPONSE TO SYPHILIS?

Recommended guidelines for the treatment of early and late syphilis have included benzathine penicillin.[90-92] In a large study of 818 patients with early syphilis (secondary or primary) published in *JAMA* in 1985, it was shown that the VDRL should drop four-fold at three months and eight-fold at six months and should be negative in at least one year for primary syphilis and two years for secondary syphilis.[93] Whether or not patients with AIDS who have syphilis respond to treatment less than those without AIDS has been in question.

The efficacy of penicillin in the treatment of syphilis is not a new one, and predates HIV as we know it. In 1950, Smith showed that 21% of patients treated with benzathine penicillin G for primary or secondary syphilis relapsed at 18 months.[94] In 1966, Short noted an 8% failure rate for benzathine penicillin G for the treatment of neurosyphilis.[95] In 1976, Tramont reported isolation of T. pallidum from the CSF of two adult patients who had received the recommended CDC dosages of benzathine penicillin G for secondary and neurosyphilis.[96]

Lukehart in 1988 also reported on the isolation of T. pallidum from the CSF of patients who had been treated with benzathine penicillin G. She studied 58 patients with untreated syphilis, 40 of whom had primary or secondary syphilis. All patients underwent lumbar puncture and CSF examination. Those patients with normal CSF findings were treated with benzathine penicillin according to the stage of syphilis. Patients with abnormal CSF findings were offered 10 days of IV penicillin. Of the 40 patients with primary or secondary syphilis, 12 had T. pallidum organisms isolated from the CSF (30%). The isolation of T. pallidum was associated with pleocytosis, elevated CSF protein and a positive CSF-VDRL. The CSF-VDRL also was positive in two of three patients with early latent syphilis (60%) and three of 15 with late latent syphilis (20%). Four patients with negative CSF findings had T. pallidum isolated from their CSF. Concurrent HIV infection was not associated with isolation of T. pallidum from the CSF or with a positive CSF serology, but it was associated with increased CSF pleocytosis. Benzathine penicillin G failed to cure three of four patients with secondary syphilis from whom T. pallidum was isolated before treatment. These three were HIV positive; the other later became HIV positive.

Lukehart inoculated rabbits with the organism to determine a cure. Her study is significant in that it shows that CNS invasion by spirochetes in both primary and secondary syphilis is quite common. In normal immunocompetent hosts, the host response plus benzathine penicillin G may be adequate to effect cure, but in patients who are immunocompromised, the standard treatment may be inadequate as manifested by failure to eradicate the organism in patients with HIV.[97]

Studies questioning the efficacy of penicillin G for syphilis are listed in Table 1. Most of these studies addressed the failure of benzathine penicillin G in the treatment of neurosyphilis, but some addressed primary and/or secondary syphilis and include studies by Smith 1950, Schroeter 1972, George 1988, and Fowler 2001.[59,94,98,99] Studies addressing the efficacy of penicillin in the treatment of syphilis in patients co-infected with HIV include: Berry in 1987, Hicks in 1987, Johns in 1987, Lukehart in 1988, and Yinnon in 1996.[57,60,97,100,101] Most of these studies showed decreased efficacy; however, the case report by Hicks noted proper response to benzathine penicillin G. Decreased serologic response to syphilis in HIV patients is noted by Hicks in 1987 and Yinnon in 1996.

It should be noted that the serologic response to therapy, though often less predictable in HIV positive patients than in HIV negative patients, does not necessarily indicate a poorer clinical response.[86] A lack of correlation between loss of a positive TST and HIV was noted by Augenbraum1998.[60,89,100] In general, what these studies have shown is that benzathine penicillin G may be inadequate treatment for neurosyphilis and for patients with syphilis and HIV infection. They also show that patients may not manifest typical manifestations and may be seronegative with T. pallidum infection especially in the presence of HIV co-infection.

In the retrospective study by Yinnon in 1996, he looked at 64 HIV-positive patients with syphilis and 64 patients with syphilis who were HIV negative.[100] All 16 patients with symptomatic syphilis were cured and no patient developed clinical signs

of neurosyphilis during the 12-month follow-up period. Twenty-nine of 52 (56%) of HIV positive patients with early or late syphilis did not have a four-fold decrease in RPR six months after treatment compared with 20 (38%) of matched controls. They concluded that patients with syphilis who are HIV positive, are less likely to experience serologic improvement after recommended therapy than patients with syphilis who are HIV negative. Patients with early syphilis and HIV in this study received three doses of penicillin as opposed to the recommended one by the CDC.[99] Augenbraun, however, as previously noted in his prospective study involving 525 patients to evaluate the response of early syphilis to benzathine penicillin G, was unable to demonstrate an association between the loss of serologic reactivity with HIV status.[89]

One of the most devastating aspects of syphilis are the late effects on the CNS and cardiovascular system. The heart manifestations are usually readily seen and infrequent; however, the CNS, as previously stated, may allow organisms to survive for years, and the standard treatment at times does not eradicate the organism, especially in the HIV-positive patient. The basis for using benzathine penicillin G is actually based on its long half life, lack of toxicity, and the fact that T. pallidum divides every 30 hours. What is troubling is that most of the studies from which this is based used aqueous or procaine penicillin G intravenously.[102] Most investigators have routinely ignored treatment failures, and the fact that benzathine penicillin G is not uniformly effective.[97,98,101-104] Research trials did not use cultured T. pallidum before and after treatment (which necessitates rabbit inoculation), and therefore, the results are implied.[102]

The Clinical Effectiveness Group's National Guideline for the Management of Early Syphilis (1999) state that in cases where neurosyphilis cannot be excluded, regimens that achieve treponemicidal levels of antimicrobials in the CSF should be the treatment of choice. They recommend procaine penicillin G 2.4 MU daily plus probenecid 500 mg four times daily for 17 to 21 days.[90] In the guidelines for late syphilis (1999) by the same group, they mention that neurosyphilis should be treated with procaine penicillin 1.8 to 2.4 mu daily plus probeneicid for 17 to 21 days or alternatively benzylpenicllin 18-24 million units daily as 3 to 4 million units iv every four hours for 17 to 21 days.[91]

The CDC (MMWR) in "Sexually Transmitted Diseases Treatment Guidelines 2002" note that HIV-infected patients with early syphilis may be at increased risk for neurologic complications and higher failure rates. They feel that the risks are "likely" minimal and recommend the same treatment regimen for early syphilis as in patients without HIV co-infection. They do note that some experts would recommend three weekly doses of benzathine penicillin G for primary and secondary syphilis for patients with HIV as opposed to a single dose of benzathine penicillin G 2.4 mu IM. HIV infected patients should be followed up at 3,6,9,12, and 24 months with a VDRL. If they fail treatment, they should be retreated as if they were HIV negative—they should have a CSF examination and retreatment. Early latent syphilis in HIV-infected patients should be treated the same as HIV negative patients with primary and secondary syphilis and patients with late latent syphilis or syphilis of unknown duration should have a CSF exam before treatment.[92]

In summary, syphilis may be more aggressive in patients with HIV; the latency period may be decreased; and, benzathine penicillin G may be less effective in syphilitics with co-infection with HIV.[57]

CONCLUSION

Syphilis and HIV infection have tremendous historical significance, especially for African Americans. Syphilis has been studied for centuries and the natural history of syphilis described before the Tuskegee Syphilis Study. Cases of AIDS have been described dating back at least to 1979. Cellular and humoral immune responses exist for both syphilis and HIV. The prevalence of HIV infection is high in syphilitics, and the seroprevalence of co-infection is highest in African Americans. Co-infection of syphilis and HIV can dramatically affect the clinical manifestations and course of either disease. Risky sexual practices among HIV-positive persons is of concern. Targeted prevention efforts and prompt treatment and prevention of syphilis and other STDs may positively impact the incidence and seroprevalence of syphilis and HIV co-infection.

Table 1. STUDIES OF SYPHILIS TREATMENT RESPONSE, SEROLOGY, CLINICAL MANIFESTATIONS WITH HIV CO-INFECTION

Author/year	Design/Methods	Results	Conclusions
Smith [94] 1956	Compared benzathine penicillin G2.5 mu (274 pts. with pri & sec syphilis) with procaine penicillin and aluminum monosterate (581 pts. with secondary syphilis). Studied 47 pts with asymptomatic neurosyphilis given 2.4 or 2.5 pen G and 53 pts given other penicillin preparations (aqueous, PAM). Used pretreatment CSF cell counts and also followed the treatment response of the CSF cell counts to treatment.	Most pts. became seronegative in two years. Either penicillin more than 92% effective for secondary and nearly 100% for primary. Pen G 71% effective at three months if initial CSF count 20-99, and 45% effective if initial count >100. By 18 months 21% of pts treated with benzathine pen G had relapsed compared to 10.5% treated with other pen G preparations.	It may be necessary to increase the dosage of 2.5 million units of benzathine pen G for treatment of asymptomatic neurosyphilis and for apparent latent syphilis if spinal fluid evaluation is not available.
Short [95] 1966	Review and Prospective Study 26 pts with active neurosyphilis were given benzathine pen 2.4 mu at the time of diagnosis and another 2.4 after seven to 10 days. If possible CSF exams were repeated at 6, 12,18 and 24 months. Criteria for active neurosyphilis was +STS in CSF and elevated CSF white cell count.	Two of 26 pts. failed treatment for an 8% failure rate. Most reviewed studies had failure rates of 9.5 to 10%.	The failure rate of benzathine pen G is close to 10% for active neurosyphilis.
Schroeter [99] 1972	Prospective comparative efficacy study of penicillin, erythromycin and tetracycline for early syphilis. Selection of cases were limited to dark-field positive lesions of primary	Failure rate for benzathine pen G 2.4mil units at 12 months, 18 months, 24months =3.5% Aqueous procaine pen G 4.8mil 12 months.18 months.24 months =2.5%	Efficacy of penicillin similar to earlier studies.

	or secondary syphilis. 566 pts randomized to one of six different treatment arms Post treatment VDRL was done monthly.		
Tramont [104] 1976	Case Report Two patients with neurosyphilis and secondary treated with benzathine pen G. Pt. #1 was treated with 1.2 m.u. benzathine pen g IM 3x week for three weeks. Pt #2 treated with 4.8 mu benzathine pen G IM.	CSF from two pts inoculated into rabbits who developed orchitis. This treatment failure resolved with IV treatment.	Demonstrated cases where acqueous penicillin IV eradicated syphilis where benzathine pen G had failed.
Mohr [105] 1976	Prospective Study 15 pts with +STS in serum and CSF. Two were given IV penicillin and 13 given benzathine pen G.	CSF pleocytosis persisted in 5 of 13 in the benzathine pen G group and none in the IV penicillin group.	There is a need to reassess the currently recommended penicillin regimens and adopt regimen consisting of large doses of IV penicillin for the treatment of neurosyphilis.
Green [103] 1980	Case Report Pt received 2.4 m.u. benzathine pen g weekly for three weeks.	Progression of neurosyphilis with treatment of 7.2 mu benzathine pen g (total dose). Neurosyphilis resolved with IV penicillin.	Validates concerns over adequacy of benzathine pen G in the treatment of neurosyphilis. Neurosyphilis should be treated with larger amounts of parenteral penicillin as opposed to benzathine penicillin regimens.
Cuddy [56] 1982	Review	Examined many of the above studies.	Penicillin G may be ineffective at times. Though it continues to serve a useful function in neurosyphilis, its use should probably be restricted to specific situations.
Berry [101] 1987	Case Report HIV + male with secondary syphilis.	Pt. was treated with 2.4 of benzathine pen G for secondary syphilis. The patients symptoms and rash resolved. The VDRL decreased at 3 months but after 5 months the patient	Pen G resulted in treatment failure. Benzathine pen G doesn't achieve treponemicidal levels in the CNS.

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		developed a left CVA and evidence of meningovascular syphilis.	
Hicks[60] 1987	Case Report HIV + male with secondary syphilis.	VDRL and FTA were repeatedly negative. Diagnosis required a skin biopsy.	The pt. responded appropriately to benzathine pen G.
Johns[57] 1987	Case Report Four cases of neurosyphilis in HIV positive patients	Two pts. developed neurosyphilis despite having received previous treatment with benzathine pen g	HIV may alter the natural course of syphilis.
George[98] 1988	Case Report 28 y/o male with primary syphilis.	He was treated with benzathine pen G 2.4 mu. and had a recurrence of the chancre at 24 days. A repeat darkfield on chancre showed spirochetes.	Treatment failure with pen G
Lukehart[97] 1988	Prospective Study 58 patients with untreated syphilis had LP with CSF inoculated into rabbits. All received ben pen according to stage of syphilis.	12 of 40 with primary and secondary syphilis had TP isolated from CSF before treatment. Two of 3 with early latent and 3 of 15 with late latent syphilis also had +CSF VDRL, pleocytosis but no TP. Co-infection with HIV was not associated with isolation of T. pallidum or reactive CSF VDRL. Three of 4 pts. with secondary syphilis and TP isolated before treatment failed cure with benzathine pen g and all three pts.who failed treatment were HIV positive.	CSF invasion is common in early syphilis and apparently independent of HIV status. Pts. with HIV may show reduced efficacy to benzathine pen g.
Van der Valk[106] 1988	Prospective Study Objective: to determine penicillin concentrations in the CSF of patients treated with procaine penicillin. 40 patients asymptomatic with syphilis, 10 with neurosyphilis.	Subtreponemicidal CSF levels found in 17 pts, 4 of whom had neurosyphilis.	Pts. should be treated with IV pen for symptomatic neurosyphilis.

	Patients were treated with procaine penicillin 2.4 mu qday IM for 10 days		
Yinnon [100] 1996	Retrospective Case Controled Study Objective: to assess the effect of HIV infection on the serologic response to treatment of syphilis. 64 HIV +, 64 HIV – patients with syphilis. All patients with HIV received three doses of benzathine penicillin G and other patients received the CDC recommended treatment.	All 16 patients with symptomatic syphilis were cured and no patient developed clinical signs of neurosyphilis during the 12 month follow up period. Twenty-nine of 52 (56%) of HIV positive patients with early or late syphilis did not have a fourfold decrease in RPR six months after treatment compared with 20 (38%) of matched controls. No unique characteristics identifying patients who did not respond serologically could be established. The HIV positive patients with initial RPR less than 1:32 experienced a significantly slower decrease in RPR at 12 months than did the controls.	They conclude that patients with syphilis who are HIV positive are less likely to experience serologic improvement after recommended therapy than are patients with syphilis who are HIV negative. Note that patients with early syphilis and HIV in this study received three doses of penicillin as opposed to the recommended one by the CDC.
Augenbraun [89] 1998	Prospective multicenter cohort treatment study. 525 pts. received either benzathine pen G or benzathine pen G + amoxicillin 2g and probenecid tid 10 days. MHA and FTA were followed over a year.	5% discordance between MHA and FTA with 85% of these demonstrating g a negative MHA. Over a year 9% of FTA seronegative and 5% of MHA.	Treponemal specific tests are the FTA-ABS, MHA-TP. They do not invariably remain reactive. The FTA becomes more non reactive more commonly than the MHA-TP even though the MHA-TP is less likely to be reactive in early primary syphilis. They could demonstrate no association between the loss of TST reactivity with HIV serostatus. The prevalent belief that the TST is invariably reactive from the time of infection for the life of the patient was not supported by the data.
Fowler [59] 2001	Case Report 39 y/o HIV positive black female with secondary syphilis.	Initial serologic testing with RPR was negative. FTA tests were inconclusive.	Clinical characteristics of syphilis may be altered in patients with HIV infection.

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		Scrapings of the lesions were negative for T. pallidum by direct fluorescent antibody testing. A punch biopsy of the lesion was inconclusive for spirochetes. Pt. received 2.4 mu of benzathine pen G weekly for three weeks. On followup a second fluorescent treponemal antibody test was strongly positive but the RPR remained negative. 12 weeks after treatment the lesions were unchanged and numerous spirochetes were identified by Warthin-Starry stain of the second biopsy specimen. The patient had a deficiency in B-cell subset (CD19+). Initial CD4 count and HIV RNA viral load were 81 X 10 6/L and 191,000 copies/mL.	Treatment failure may depend on the degree of immunosuppression.

PAM = procaine penicillin and aluminum monostearate
pen = penicillin
STS = serologic test for syphilis
TST=treponemal specific test, mu = million units

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