Syphilis and HIV: a dangerous combination

W A Lynn and S Lightman

HIV and syphilis affect similar patient groups and co-infection is common. All patients presenting with syphilis should be offered HIV testing and all HIV-positive patients should be regularly screened for syphilis. Syphilis agent may enhance the transmission of the other, probably through increased incidence of genital ulcers. Detection and treatment of syphilis can, therefore, help to reduce HIV transmission. Syphilis may present with non-typical features in the HIV-positive patient: there is a higher rate of symptomless primary syphilis and proportionately more HIV-positive patients present with secondary disease. Secondary infection may be more aggressive and there is an increased rate of early neurological and ophthalmic involvement. Diagnosis is generally made with serology but the clinician should be aware of the potential for false-negative serology in both primary and, less commonly, in secondary syphilis. All HIV-positive patients should be treated with a penicillin-based regimen that is adequate for the treatment of neurosyphilis. Relapse of infection is more likely in the HIV-positive patient and careful follow-up is required.


Syphilis and HIV are both transmitted sexually and so it is no surprise that a substantial number of people are infected with both agents. HIV has several effects on the presentation, diagnosis, disease progression, and therapy of syphilis. Syphilis may increase the risk of HIV transmission and acquisition by causing genital ulcers. Genital ulcer disease is linked to increased risk of HIV infection and is most commonly due to herpes simplex virus (HSV) in both HIV positive and negative patients. Syphilis continues to affect large numbers throughout much of the world and the past 5 years has seen a number of outbreaks. HIV makes it more likely for syphilis to present with non-typical features. Thus, it is important for medical practitioners to be aware of how syphilis may present in patients with underlying HIV infection and its implications for treatment and follow-up.

Controversy has surrounded the area of HIV and syphilis co-infection. Some have argued that syphilis has a different clinical presentation and is more aggressive in people with HIV; others suggest there is little difference. There are differences in the interpretation of serological tests for syphilis in the HIV positive but how often does this matter clinically? Finally, some recommend that all HIV-positive patients should be treated as if they had neurosyphilis regardless of the stage at which they present, although the feared epidemic of neurological involvement has not materialised. This article will try to answer some of these questions by reviewing the epidemiology, diagnosis, clinical features, and management of syphilis in people infected with HIV. Congenital syphilis was reviewed in the Lancet Infectious Diseases in 2002 and will not be discussed here in detail.

Epidemiology

WHO estimates that approximately 349 million people are actively infected with a treatable sexually transmitted disease. Of these, estimates from 1999 suggest an annual rate for syphilis of approximately 12 million active infections. Almost two-thirds of these cases are in sub-Saharan Africa and south/southeast Asia. Recent outbreaks have been reported from many countries on all continents. In sub-Saharan Africa between 2 and 17% of women test positive for syphilis in antenatal clinics and rates of HIV co-infection are very high. In North America and western Europe the incidence of syphilis is much lower at less than 5/100 000 of the population or less. There was steady decline in the incidence of syphilis in both Europe and the USA during the second half of the last century, leading to suggestions that endemic syphilis might even be eradicated in these countries. The past few years, however, have seen an upsurge in syphilis in Europe and isolated outbreaks in North America. The reasons underlying this reversal are complex but include migration of people from high-prevalence countries, population mixing, changes in risk behaviour including the use of the internet to meet partners, use of recreational drugs, and a reduction in safe sex practices in gay men.

In the UK the incidence of syphilis fell dramatically through the 1980s to less than 1/100 000 of the population. A rise in syphilis incidence has been seen since 1996 with most cases occurring in young men. Over the same time period there has also been an increase in new HIV diagnoses in the UK increasing the likelihood of HIV and syphilis co-infection (figure 1). In 2002 syphilis rates for men in England and Wales ranged from 0.5/100 000 in rural areas to more than 2.0/100 000 in metropolitan districts with particularly high rates in Brighton, Manchester, and London. There has been a smaller but still significant rise...
in syphilis in women with by far the greatest number of cases reported from London. An enhanced syphilis surveillance programme run by the UK Health Protection Agency indicated that, in 2002, 57% of reported cases were from gay men, a proportion of whom are co-infected with HIV. More detailed analysis of the outbreak in Manchester highlighted unprotected oral sex as a major risk factor for syphilis transmission amongst gay men. Many of these men followed safe sex practices including the use of condoms for anal intercourse but were unaware that syphilis could be orally transmitted.

The rate of HIV and syphilis co-infection will vary depending on the prevalence of both infections in the community or the patient group being studied, along with individual risk factors. Blocker and colleagues reviewed 30 studies that looked at HIV rates in people with syphilis in the USA. They reported an overall median seroprevalence for HIV of 15.7% (27.5% in men and 12.4% in women). This gave an odds ratio for having HIV of 8.8 for men and 3.3 for women presenting with syphilis. Furthermore, much higher rates of HIV co-infection were detected in relation to specific risk factors, for example intravenous drug use (22.5–70.6%) and gay sex (68–90%). In one Spanish study of 1161 HIV-positive patients followed-up for 38 months the baseline syphilis seroprevalence was 13% and a further 4% acquired syphilis (68–90%). The German AIDS Study Group found 151 cases of active syphilis in 11368 HIV-positive patients (1–3%). Of the 151 active cases 17.2% were primary syphilis, 36.4% secondary syphilis, 16.6% neurosyphilis, and 25.2% latent syphilis. These figures cannot be applied to all populations due to variation in underlying prevalence rates and risk factors but stress the high rates of co-infection and ongoing risk of disease acquisition. All patients presenting with a sexually transmitted infection should be offered HIV testing and given advice on HIV prevention. Similarly all people presenting with HIV should be screened for syphilis and re-screened regularly during follow-up. Reinfection with syphilis may occur and all patients should receive advice on safe sexual practices. Current UK recommendations are for annual serological testing for syphilis in all HIV-infected people with consideration for more frequent screening in the event of a local disease outbreak.

The close interaction between HIV and syphilis epidemiology is illustrated by Chesson and colleagues’ analysis of available data from the US Centers for Disease Control (CDC) on the incidence of syphilis in 40 US states over a 14-year period. There was a 90% reduction in syphilis cases between 1990 and 2000. Mathematical modelling suggested that AIDS-related mortality was responsible for between one-third and half of this reduction. Chesson and colleagues postulate that the decline in HIV mortality since the development of antiretroviral therapy, coupled with continued high-risk sexual behaviour in HIV-infected people may be responsible for recently reported rises in syphilis transmission.

Syphilis, through genital ulcer disease, may increase the risk of HIV transmission. For example, one mathematical model has suggested that approximately 1000 additional cases of heterosexual HIV transmission occur annually in the USA as a result of syphilis. Using syphilis and HIV co-infection data from black Americans in 2000, Chesson et al have calculated that 545 cases of HIV transmission were facilitated by syphilis in couples discordant for HIV. The additional health cost of the 545 potentially preventable HIV infections was estimated at US$113 million. These data come from the USA where the prevalence of syphilis is much lower than in many countries with a high burden of HIV infection. These data emphasise the need to include the surveillance, prevention, and
treatment of syphilis and other sexually transmitted infections within HIV-control programmes. This is particularly relevant to countries with a high prevalence of syphilis, genital ulcer disease, and HIV.

Diagnosis

The key to syphilis recognition is a full examination by a skilled medical practitioner familiar with the protean manifestations of the infection. This examination should include all of the skin and mouth as well as the genital region. If syphilis is not suspected then the opportunity for early diagnosis and treatment and public-health intervention will be lost.

Serological diagnosis of active syphilis

The mainstay of diagnosis of syphilis in the non-HIV infected adult is serology,12,28,29 Serological tests may be negative in early primary syphilis and here direct identification of the organism by dark field microscopy or within tissue biopsies may confirm the clinical diagnosis.30 Serological investigations are divided into non-treponemal antibody tests, such as the Venereal Diseases Research Laboratory (VDRL) or the rapid plasma reagin (RPR), and specific treponemal antibody tests (table 1).4,29 In general a non-treponemal test plus a specific treponemal tests is used for screening in both HIV-negative and positive people.20

Serological testing in the HIV-negative patient

In the HIV-negative patient, around 14% have negative serology at presentation with primary syphilis but fewer than 1% will have negative tests with secondary disease.28 Without therapy non-treponemal antibody titres peak during secondary syphilis and then gradually decline, so that up to 20–25% of patients with untreated late latent syphilis may have a negative non-treponemal antibody test. Specific treponemal antibody, however, persists in almost all patients with a sensitivity of 97–98% in late syphilis.3 After successful antimicrobial therapy, non-treponemal serological tests generally become negative within 1 year. However, a small proportion of patients (fewer than 5%) have persistently positive results despite effective therapy and are referred to as “serofast”. By contrast, specific treponemal antibody tests remain positive for life in almost all cases.

False positive non-treponemal antibody results are seen in a range of conditions associated with phospholipid antibody production including autoimmune diseases, pregnancy, and several infectious agents including other spirochaetal infections and HIV.33 False-positive non-treponemal antibody titres are generally low, are not persistent, and the patients have a negative specific treponemal antibody test. False-negative non-treponemal antibody tests are seen in approximately 2% of patients and are due to the prozone effect where blocking antibodies or very high antibody titres interfere with the assay.21 The prozone effect is less common with newer tests but it is important that all physicians testing patients for syphilis are aware of the possibility of a false-negative test. The prozone effect is easily avoided by testing diluted serum.

Table 1. Sensitivity and specificity of serological tests in syphilis in HIV-negative people

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary sensitivity (%)</th>
<th>Secondary sensitivity (%)</th>
<th>Tertiary sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPR</td>
<td>86</td>
<td>100</td>
<td>70</td>
<td>98</td>
</tr>
<tr>
<td>VDRL</td>
<td>80</td>
<td>100</td>
<td>75</td>
<td>98</td>
</tr>
<tr>
<td>Specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPHA</td>
<td>80</td>
<td>100</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>MHA-TP</td>
<td>76</td>
<td>100</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>FTA-ABS</td>
<td>84</td>
<td>100</td>
<td>96</td>
<td>98</td>
</tr>
</tbody>
</table>

RPR=rapid plasma regain; VDRL=venereal disease research laboratory; TPHA=Treponema pallidum haemagglutination assay; MHA-TP=microhaemagglutination assay—Treponema pallidum, FTA-ABS=fluorescent treponemal antibody absorption test. Adapted from GR Kinghorn with permission.4

Serological testing in the HIV-positive patient

Case reports have identified potential differences in serological testing for syphilis between HIV-negative and HIV-positive patients although the clinical importance of these differences remains unclear. These differences include an increased rate of negative serological tests in both primary and secondary syphilis,33,34 increased false-negative non-treponemal antibody tests due to the prozone effect,35,36 high rate of failure to clear non-treponemal antibody after therapy (serofast),37 and seroreversion to negative of specific treponemal antibody tests after therapy.40 The difference in serological response in HIV-positive patients is not clearly related to CD4 count but similar events have been reported in non-HIV infected immunocompromised patients.35 False-positive non-treponemal antibody tests are encountered more frequently in the HIV-positive individual and may be seen in up to 11% of cases.35 Reinfection with syphilis may occur in HIV-negative or positive patients. It may be difficult to distinguish on serological grounds between the patient who is serofast after effective therapy, treatment failure, and reinfection.40

Patients can present with the typical features of primary or even secondary syphilis but have negative non-treponemal and treponemal antibody results.40 Furthermore, in the German study quoted earlier, of 151 HIV-positive patients with syphilis, false-negative VDRL titres were seen in 11 patients with non-primary syphilis (7.3%), and false-positive specific treponemal antibody tests in 17 cases (11-25%, Treponema pallidum haemagglutination in one case and 19S-IgM-FTA-ABS-tests in 16).40 By contrast, Gwanzura et al41 studied 709 serum samples from 580 patients in Zimbabwe using the RPR, VDRL, and T pallidum haemagglutination. The prevalence of HIV in the cohort was 19.8% and 78 cases of active syphilis were detected. In particular, the negative predictive value of combined serology was greater than 99% with no difference between the HIV-negative and positive patients.
Thus, although individual case reports identify patients presenting with manifestations of syphilis with negative serology, there are insufficient data to warrant an alteration to using standard serological tests for syphilis screening in HIV-positive patients.20 However, it is important that clinicians involved in the care of people with HIV are aware that occasional patients may present with manifestations of syphilis and have negative initial syphilis screening tests. Such patients presenting with suspicious genital or other lesions must have investigations aimed at direct identification of the organism—i.e., dark-field microscopy of material from lesions or by tissue biopsies.21 All patients should be referred to a clinic where such facilities are available and specialist expertise for the diagnosis and management of syphilis is available.

Clinical manifestations of syphilis in the HIV-positive patient

Typically syphilis occurs in three phases—namely primary, secondary, and tertiary disease. However, this is a gross oversimplification and the clinical presentation of syphilis is extremely variable over many years (figure 2).4 Several differences have been reported in the manifestations of syphilis in HIV-positive patients. In particular there seems to be a shift from presentation with primary to secondary disease and more aggressive disease progression. Furthermore, HIV itself or opportunistic infections may confuse clinical and diagnostic findings.

In the HIV-negative patient primary syphilis generally develops after an incubation period of 21 days with a painless chancre at the site of inoculation. This pattern holds true for syphilis in the HIV-positive patient but primary disease is more likely to be symptomless and HIV-positive patients more often present with secondary or latent infection. For example, the UK enhanced surveillance programme in London reported on the presentation of syphilis in HIV-negative (n=215) and HIV-positive (n=311) men. Primary syphilis was diagnosed in 42% and 27% and secondary syphilis in HIV-negative (n=215) and HIV-positive (n=311) respectively.15 It is important to recognise that with the relative increase in importance of oral sex in transmission of syphilis the primary lesion may not be in the genital area (figure 3).

Cutaneous

Skin lesions are a common manifestation of secondary syphilis (72%)6 5 and may be the presenting feature. A number of different types of skin lesions are recognised together with lymphadenopathy, malaise, arthralgia, and fever. The most common type is of a diffuse maculopapular rash which typically appears about 6 weeks after the primary lesions and signifies haematogenous spread of T pallidum.40 A generalised macular rash with palmar-plantar involvement may also occur (figure 4)40 but other types may occur such as lichenoid,51 papular, papulosquamous, ulcerated, and urticarial lesions with hair loss varying from alopecia52 to involvement of the eyebrows and even total loss of body hair.52 Nodular and annular53 skin lesions over the face, back, and limbs are reported as are large plaques on face, neck, and upper extremities.54 Nodular skin lesions can be seen in secondary or tertiary syphilis and clinical and histological stages may overlap.55,56 Vesiculobullous skin lesions may occur in congenital syphilis.57

Due to the varied appearances of syphilis manifestations, and because several other diseases may cause similar appearances, biopsy is common and often establishes the diagnosis. Histologically a wide range of changes is seen. Treponemes are seen in both the epidermis and dermis.58 Plasma cells and lymphocytes (which can be CD4+ lymphocytes, CD8+ lymphocyte, or histiocytic in type)59 can be seen around blood vessels which may have marked endothelial swelling and proliferation associated with increased levels of vascular endothelial derived growth factor.60 No correlation is seen between types of skin lesion and VDRL titre. Nodular lesions may show sarcomatous granulomata with lymphocytes, histiocytes, eosinophils, plasma cells, and multinucleated giant cells.61 In patients with concomitant HIV infection, syphilis is only one of many possible causes of skin rash. Although the skin lesions of syphilis may look similar in HIV-positive or HIV-negative patients, they may also look different. The rash may seem atypical, resulting in the incorrect diagnosis of another infection or malignancy.62-64 Biopsy is commonly needed to establish the diagnosis but the histological manifestations of secondary syphilis are very variable even in the absence of HIV.65 There may also be increased frequency of the lues maligna or the ulceronodular type65-67 and the disease course may be more aggressive.68-70 Co-pathologies such as Kaposi’s sarcoma and other skin lesions may also occur. With the possibility of falsely negative serology for syphilis in HIV infection, the diagnosis of syphilis as a cause of skin lesions may be missed. Biopsy remains the key to making the diagnosis in these situations.71
Musculoskeletal manifestations can be associated with congenital, secondary, and tertiary syphilis and can mimic a wide range of rheumatic and systemic diseases with joint involvement. Typically syphilitic arthritis is a chronic symmetric polyarthritis. There are several causes of sexually transmitted arthritis and arthralgia, inflammatory arthritis, and neuropathic arthritis may occur during any stage of congenital or acquired syphilis. Syphilitic synovitis responds well to antibiotic therapy, but neuropathic lesions cannot be treated effectively.66

Arthritis can also be the initial presentation of syphilis with HIV infection and synovitis may occur in the presence of marked CD4+ lymphocyte depletion. Difficulties occur in diagnosis in HIV infection because of the negative syphilis serology that can occur but also because of autoimmune abnormalities that include positive rheumatoid factor, nuclear antibody, and double-stranded DNA. The arthritis responds well to treatment with penicillin even with HIV infection.68

Clinically significant osteitis and osteomyelitis are rare complications of primary or secondary syphilis in patients who are and are not infected with HIV69 but bone pain is a common feature of bone involvement and lytic lesions may occur (figure 5).70 Osteitis of the skull has been reported as a presenting feature of HIV infection as has ulnar osteitis complicated by a pathological fracture, which responded to high-dose intravenous penicillin G therapy and surgical intervention.70

Central nervous system
Patients co-infected with syphilis and HIV present a diagnostic and therapeutic challenge since both syphilis and HIV infection can have neurological involvement, which can be very variable.71–74 This makes the interpretation of cerebrospinal fluid (CSF) analysis, on which the diagnosis of neurosyphilis is based, particularly problematic.

Neurosyphilis may affect the brain, spinal cord, or peripheral nerves. In HIV-negative patients, neurosyphilis can present in several ways. Neurological involvement may occur in the early post-primary stage or after a gap of many years (figure 2). In 10% of patients it is symptomless and the peak incidence is 12–18 months post primary infection. Meningeal involvement can occur with the patient presenting with aseptic meningitis and acute symptoms such as headache, neck stiffness, and photophobia. Cranial nerve palsies, especially of the VII and VIII nerves, papilloedema, and neuropsychiatric features or seizures can also occur.75–78 Meninogovascular syphilis presents 4–7 years after infection and symptoms occur because of vascular ischaemia in the territory of the middle cerebral, basilar, or spinal arteries. Hence patients may present with focal neurological deficits such as hemiparesis, aphasia, or seizures. The necrotising granulomatous gummas of late syphilis within the central nervous system give rise to symptoms and signs of space-occupying lesions. Rarely parenchymatous involvement causes cognitive impairment, psychiatric symptoms, and neurological signs affecting the pupils and causing hypotonia of the face and limbs, intention tremor, and hyper-reflexia.79

The increased prevalence of neurosyphilis in HIV infection is shown in one study where incidence was 23–5% in HIV-positive patients with untreated syphilis.80 This prevalence contrasts with 10% in HIV-negative patients with untreated syphilis. In HIV infection, neurosyphilis may be symptomless but a range of presentations may also occur. All types of neurosyphilis as described above are seen including headache, hearing loss (which may be bilateral and severe),81 spastic paraparesis secondary to syphilitic meningomyelitis,82 medullary syndromes,83 stroke (which can be acute or sub-acute involving the basal ganglia or middle cerebral arteries),77,84 gait disturbances, and optic atrophy or papillary changes.85 Gummas may mimic the symptoms and signs of a space-occupying intracranial lesion including meningioma with headache and ataxia.86 Personality changes are the commonest symptom of late syphilis with HIV infection and are due to syphilitic vasculitis with lacunar infarcts. In children with AIDS, syphilis may also contribute to the neurological manifestations.87 Neurocognitive impairment is common in HIV patients but is worse in those co-infected with syphilis.87 Furthermore, co-infection with herpes viruses, toxoplasmosis, cryptococci, progressive multifocal leukoencephalopathy and other central nervous system infections may complicate the clinical and diagnostic picture in persons with underlying HIV.88

It is also suggested that HIV accelerates and changes the clinical course of neurosyphilis and that co-infection with HIV increases the incidence of the neurological complications of syphilis.89 Aggressive neurosyphilis can occur with either high or low CD4+ lymphocyte counts.90 In one recent study a CD4 count of less than 350 indicated a three-fold increased risk of neurological involvement in the HIV-positive patient with syphilis.91 Neurosyphilis in the context of HIV co-infection with HIV is more difficult to diagnose because HIV infection itself is frequently associated with a CSF pleocytosis.92 Significant differences were noted in CSF measurements when HIV-positive patients were compared with HIV-negative patients with syphilis,
including a higher cell count, higher protein, and lower glucose levels in the HIV-infected group.75 PCR has poor sensitivity for the diagnosis of neurosyphilis in HIV and is therefore not helpful in most patients where there is diagnostic difficulty.76

Measurement of CSF antibodies to syphilis are generally used to confirm neurological involvement. In HIV-negative patients the presence of either non-treponemal or specific treponemal antibodies in CSF indicates neurosyphilis.95 In HIV-positive patients, however, the CSF VDRL may rarely be negative despite neurosyphilis96 and when present CSF treponemal antibodies commonly persist after therapy.97 The CSF VDRL may rarely be negative in the HIV-negative patient with neurosyphilis. Caution should also be used when interpreting blood-contaminated CSF where a positive serological result may come from the blood contamination.98 The problem of neurosyphilis in HIV-positive patients has led some authorities to recommend lumbar puncture in all HIV-positive patients irrespective of the stage of syphilis.99 An alternative strategy is to ensure that all HIV-positive patients with syphilis receive a course of therapy that will achieve treponemocidal concentrations of penicillin in both serum and CSF.92 UK guidelines are that a full neurological assessment should take place in all patients and a computed tomography head scan and lumbar puncture are indicated only if clinical abnormalities are found.99

Imaging may be of help in both diagnosis and monitoring the effect of treatment. Computed tomography scanning can show the presence of multifocal, low density lesions with particular characteristics of infarction.100 Contrast-enhanced magnetic-resonance imaging (MRI) can show the extent of involvement by neurosyphilis and may show patchy contrast enhancement involving the basal ganglia and middle cerebral artery territories or a mass which may resolve on treatment.101 MRI is particularly useful in diagnosing spinal cord involvement with syphilis.102,103

Retrospective studies of the treatment of neurosyphilis in the presence of HIV infection suggest that for 23–60% of HIV-infected patients current neurosyphilis therapy with penicillin G does not work.35,97,101 However, the risk of neurological sequelae in HIV-infected patients with early syphilis and abnormal CSF treated with penicillin is unknown.23 Standard treatment is with high-dose penicillin100,106 but there may be persistence.107 At least 3–4 weeks of treatment are recommended.108 Ceftriaxone has excellent activity against T pallidum and has good central nervous system penetration. Case reports of effective use of ceftriaxone have been reported but data are limited and ceftriaxone is not licensed for use in neurosyphilis.109

Ocular involvement

The eyes and visual system can be affected in many different ways by syphilis but none of the signs are pathognomonic. All structures of the eye may be affected110 but the commonest manifestation is uveitis (intraocular inflammation). Uveitis can occur at all stages of syphilis including primary infection110 and may spontaneously resolve but the relapse rate is high without treatment. It may also occur in tertiary syphilis affecting 2.5–5% of the 30% untreated patients that progress.112 Several different types of uveitis—anterior uveitis, posterior uveitis, and keratouveitis—are recognised. Patients with posterior uveitis may have vitritis, focal retinitis, chorioretinitis (figure 6),113,114 periphlebitis, retinal haemorrhages, papillitis,115 and exudative retinal detachments.116

Many other signs of intraocular involvement may be seen including optic neuritis, neuroretinitis, and arterial and venous occlusion.117 Patients with neuroretinitis may notice painless fluctuating visual loss and floating spots, which may be associated with retinitis, papillitis, vitritis, and sometimes anterior uveitis. Isolated optic neuritis with unilateral visual loss may occur with signs of meningeal inflammation without any associated uveitis or retinal

---

**Figure 4. Involvement of the palm (A) and soles (B) with a lichenified scaly rash due to secondary syphilis in an HIV-positive man presenting with panretinitis. The rash had been present for several weeks and was thought to be psoriasis by a rheumatologist who was seeing him for a “sero-negative” arthropathy.**
vasculitis. Paracentral scotomas and blind-spot enlargement related to posterior pole lesions and papillitis are the most common visual field defects. The orbit may also be involved. Most patients recover well with penicillin treatment but visual loss can occur from macular oedema and retinal ischaemia from the endarteritis. However, not all ocular syphilis can be cured with neurosyphilis regimens and many more will relapse with less intense regimens.

HIV infection itself can have many effects on the eye and can cause uveitis as well as having associated infections, malignancies and drugs that can cause uveitis. Severe ocular manifestations and an accelerated natural course of syphilis along with neurosyphilis may be associated with HIV infection. Eye disease may be the presenting symptom/sign of co-infection with HIV. There are differences in the uveitis seen in patients with syphilis co-infected with HIV—the uveitis may be more severe in the HIV-positive group—panuveitis is more common than isolated anterior uveitis, and a dense vitritis occurs despite a low CD4+ lymphocyte count, but this usually responds well to treatment. Papillitis, optic neuritis, and retrobulbar optic neuritis may all be worse in HIV-positive versus HIV-negative patients and there may be concomitant central nervous system disease.

Syphilis serology may be negative when patients present with inflamed eyes and co-infection with syphilis and HIV. This may delay the diagnosis of syphilis since none of these signs are specific for syphilis and if investigations are negative, it is very likely that these patients will be given systemic corticosteroids with severe sequelae instead of disease resolution with penicillin. With penicillin treatment 67% of patients have improved vision with reduced inflammatory signs in 92%, but relapses of ocular disease may also occur despite treatment.

Cardiovascular
By contrast with neurosyphilis there have been few reports of vascular involvement in HIV-positive patients. Arterial aneurysms can be seen in HIV infection and commonly involve the common carotid artery and abdominal aorta. These may be multiple and can also be associated with syphilis. In HIV-negative patients vascular disease is one of the late manifestations of syphilis (figure 2). Thus, it is possible that the paucity of reports of vascular syphilis in HIV-positive patients is simply due to the relatively short duration of infection and to the high rate of detection and treatment of latent syphilis in HIV.

Other systems
Oral lesions can occur in syphilis with and without HIV infection and are usually seen in secondary disease (figure 7). Rarely the lung and pleura can become involved. Spirochetes may be detected in pleural fluid associated with pneumonia even in patients with good CD4+ lymphocyte counts. Nephrotic syndrome is a recognised complication of HIV infection and progresses to renal failure without antiretroviral therapy. In association with syphilis, however, it is reversible with treatment.

Treatment of syphilis
Penicillin remains the mainstay of therapy for all stages and sites of syphilis and in all patient groups. Guidelines vary (table 2) but the general principle is one of maintaining prolonged serum treponemocidal concentrations. In HIV-negative
patients with early syphilis (less than 2 years’ duration) it is not necessary either to investigate for neurosyphilis or to use therapy that achieves treponemocidal concentrations of antibiotics in CSF (table 2).20,105 For example, CDC guidelines recommend a single dose of intramuscular benzathine penicillin for primary and secondary disease.105 In late syphilis (greater than 2 years’ duration) CDC guidelines recommend CSF examination in the presence of ophthalmic or neurological signs, treatment failure, evidence of tertiary syphilis, or if the patient is co-infected with HIV.105 If CSF is normal then benzathine penicillin is still recommended but the duration of treatment is increased to three doses at weekly intervals (table 2). Benzathine penicillin does not achieve adequate CSF concentrations and so is not recommended where there is evidence of neurosyphilis.

When treating syphilis in the HIV-positive patient it is important to use a drug regimen that will achieve adequate CSF concentrations.20 This requires intravenous benzyl penicillin, which is impractical in most cases, or daily intramuscular procaine penicillin plus oral probenecid to reduce renal excretion (table 2). When benzyl penicillin or procaine penicillin has been used as first-line therapy there is a low clinical treatment-failure rate. Long-acting benzathine penicillin preparations have been reported to have higher rates of serological failure, for example 18% in one study despite augmenting the weekly benzathine penicillin injections with oral amoxicillin.138 Thus, daily intramuscular procaine penicillin plus probenecid should be the recommended first-line therapy for primary, secondary, or latent syphilis in HIV-positive patients (table 2).20 Where compliance and personal choice make this regimen untenable then weekly benzathine penicillin plus oral amoxicillin and probenecid may be considered.138 In the penicillin-allergic patient doxycycline is often used as a second-line agent. There is uncertainty about whether

<table>
<thead>
<tr>
<th>Syphilis stage</th>
<th>USA guidelines (CDC)</th>
<th>UK guidelines</th>
<th>Alternative agents in UK guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early disease (&lt;2 years, primary, secondary, and early latent infection)</td>
<td>Benzathine penicillin G 50 000 units/kg IM, up to the adult dose of 2·4 million units in a single dose</td>
<td>Procaine penicillin G 750 mg IM daily × 10 days or Benzathine penicillin G 2·4 million units IM in a single dose</td>
<td>Doxycycline 100 mg BD × 14 days Erythromycin 500 mg QDS × 14 days Amoxicillin 500 mg QDS plus probenecid 500 mg QDS × 14 days</td>
</tr>
<tr>
<td>Early syphilis in HIV-positive</td>
<td>As above, some clinicians recommend 3 doses at weekly intervals</td>
<td>Procaine penicillin 2 million units IM OD + probenecid 500 mg QDS × 17 days</td>
<td>Doxycycline 200 mg BD × 28 days Amoxicillin 2 g TDS plus probenecid 500 mg QDS × 14 days</td>
</tr>
<tr>
<td>Late latent disease (&gt;2 years since acquisition)</td>
<td>Benzathine penicillin G 2·4 million units IM weekly × 3 doses</td>
<td>Procaine penicillin G 750 mg IM daily × 17 days or benzathine penicillin G 2·4 million units IM weekly × 3 doses</td>
<td>Doxycycline 200 mg BD × 28 days Amoxicillin 2 g TDS plus probenecid 500 mg QDS × 14 days</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 h or continuous infusion, for 10–14 days.</td>
<td>Procaine penicillin 2 million units IM OD + probenecid 500 mg QDS for 17 days</td>
<td>Doxycycline 200 mg BD × 28 days Amoxicillin 2 g TDS plus probenecid 500 mg QDS × 14 days</td>
</tr>
<tr>
<td>Neurosyphilis in HIV positive</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
</tbody>
</table>

IM=intramuscular; IV=intravenous; CDC=US Centers for Disease Control and Prevention; OD=once daily; BD=twice daily; TDS=three times daily; QDS=four times daily.
adequate CSF concentrations of doxycycline are achieved but treatment failure is rare and doxycycline remains a useful agent. Erythromycin is used as a second-line agent in the HIV-negative patient but has very poor CSF penetration and should not be considered in HIV-positive patients.18 Furthermore, recent reports have described the emergence of resistance to erythromycin.19 Azithromycin is a macrolide antibiotic with activity against T pallidum. The long half-life of azithromycin allows for once-daily dosing and small studies have been encouraging.20 Caution must be expressed regarding the use of azithromycin in the light of reports of treatment failure.18

Where an HIV-positive patient has evidence of neurosyphilis, with clinical and/or imaging abnormalities plus an abnormal CSF, then high-dose intravenous benzyl penicillin may be the preferred choice. There are no clear data, however, to suggest that this is superior to intramuscular procaine penicillin plus probenecid (table 2). In both neurosyphilis and pregnancy there is no agreed alternative to penicillin. Treatment failures in neurosyphilis are likely with doxycycline and doxycycline is contraindicated in pregnancy. In this setting consideration can be given to desensitisation for penicillin allergy.20 Ceftriaxone has good treponemocidal activity and CSF penetration. In a small pilot study of HIV-positive patients with neurosyphilis ceftriaxone had been reported to be at least equivalent to procaine penicillin18 but more data are required before ceftriaxone could be routinely recommended.

Treatment of syphilis may be complicated by the Jarisch-Herxheimer reaction mediated by cytokine release induced by treponemal lysis after therapy,106 The reaction occurs within 4–24 h of penicillin administration and consists of an acute febrile illness and may include increased inflammation at the site of clinical disease. If the Jarisch-Herxheimer reaction is severe or involves a critical body site then corticosteroids are indicated.106 Jarisch-Herxheimer reactions have been reported in HIV-positive patients but do not seem to be more severe or frequent than in HIV-negative patients.

The vast majority of HIV-negative patients will show a steady fall in serum non-treponemal antibody levels and have negative VDRL or RPR tests within 1–2 years of effective therapy. Persistence of serum antibodies is much more likely in HIV-positive patients and does not necessarily indicate inadequate treatment. Current guidelines suggest repeating serology at 3 month intervals for the first year after treatment and then annually for life.21 A fourfold rise in serum VDRL or RPR titre should be considered to indicate relapse or reinfeciton, and retreatment offered.

Best practice would be for all people with syphilis to be counselled regarding safer sexual practices. They should be also be referred for partner notification and contact tracing.

Future prospects
So what does the future hold? It is remarkable that penicillin remains the mainstay of therapy and there is little prospect that newer antibiotics will displace penicillin in the near future particularly following the emergence of macrolide resistance. An effective vaccine would offer great hope but insufficient research efforts have directed against syphilis. Despite some successes213 our understanding of the determinants of protective immunity to T pallidum remain poor with little prospect for an effective vaccine in the near future. Unless there is a concerted global and politically supported public-health drive to reduce the transmission of syphilis then syphilis will continue to lead to substantial morbidity and further fuel the HIV pandemic.

Conflicts of interest
SL is a member of the international advisory board of The Lancet.
Syphilis and HIV

Review

115 Jumper JM, Machemer R, Gallemore RP, Jaffe GJ.
114 Friberg TR. Syphilitic chorioretinitis.
103 Srivastava T, Thussu A. MRI in syphilitic
113 de Souza EC, Jalkh AE, Trempe CL, Cunha S,
des Souza EC, Jalkh AE, Trempe CL, Cunha S,
112 Deschenes J, Seamone CD, Baines MG. Acquired
111 Spoor TC, Ramocki JM, Nesi FA, Sorscher M.
110 Aldave AJ, King JA, Cunningham ET Jr. Ocular
109 Shann S, Wilson J. Treatment of neurosyphilis with
108 Guiloff RJ, Tan SV. Central nervous system
influence of human immunodeficiency virus status
107 Spehn J, van der C, Ramocki JM, Nesi FA, Sorscher M.
106 MSSVD. UK guideline for the management of late
3, 2003).
105 USA Centers for Disease Control and Prevention.
104 Halperin LS, Lewis H, Blumenkranz MS, Gass JD,
103 Kuo IC, Kapusta MA, Rao NA. Vitritis as the
102 Kikuchi S, Shinpo K, Niino M, Tashiro K. Subacute
syphilitic meningomyelitis with characteristic spinal
101 Tien RD, Gean-Marton AD, Mark AS. Neurosyphilis
erebrospinal fluid abnormalities after treatment of
100 US Centers for Disease Control and Prevention.
Sexually transmitted diseases treatment guidelines
99 MSSVD. UK guideline for the management of late
December 3, 2003).
98 Halperin LS, Lewis H, Blumenkranz MS, Gass JD,
97 Browning DJ. Posterior segment manifestations of
reactive ocular syphilis, their response to a
neurosyphilis regimen of penicillin therapy, and the
96 Juniper JM, Mackenner R, Gallemore RP, Jaffe GL.
Exudative retinal detachment and retinitis associated
with acquired syphilitic uveitis. Retina 2000; 20:
190–94.
95 Halperin LS, Lewis H, Blumenkranz MS, Gass JD,
94 Weinstein JM, Lexow SS, Ho P, Spickards A. Acute
syphilitic optic neuritis. Arch Ophthalmol 1981; 99:
93–92.
93 Carrie JB, Coppepo JL, Lesel S. Chronic syphilitic
meningitis resulting in superior orbital fissure
syndrome and posterior fossa guma. A report of
92 Arraga J, Valentine T, Mauri P, Roca G, Salom R,
91 Kramer M, Lynn W, Lightman S. HIV/AIDS and the
90 Liu H, Chen SJ, Chung YM, Chioo SH, Wng WW.
Syphilitic uveitis as the initial manifestation of
89 Becerrra LL, Kisaek SM, Soriro FT, et al. Syphilitic
uveitis in human immunodeficiency virus-infected
and noninfected patients. Ophthalmolog 1989; 96:
1727–30.
Syphilitic panuveitis and asymptomatic
neurosyphilis: a marker of HIV infection. Int J STD
87 Kuo KC, Kapusta MA, Rao NA. Vitritis as the
primary manifestation of ocular syphils in patients
with HIV infection. Am J Ophthalmol 2008; 128:
306–11.
86 Zambrano W, Perez GM, Smith H. Acute syphilitic
blindness in AIDS. J Clin Neuroophthalmol 1987; 7:
1–5.
85 McGlash WM, Palidu JS, Holland S, Culbertson
84 Passo MS, Rosenbaum JA. Ocular syphils in patients
with human immunodeficiency virus infection.
83 Zamani M, Garkulik R, Curocium-stimulated
modulation of acute syphilitic posterior placoid
82 Shahaly IA, Dunn JP, Smsha RD, Jabs DA. Syphilitic
uveits in human immunodeficiency virus-infected