

CLINICAL STANDARDS FOR THE SCREENING AND MANAGEMENT OF ACQUIRED SYPHILIS IN HIV-POSITIVE ADULTS

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1. Introduction

1.1 Background

It is increasingly recognised that HIV-positive individuals continue to remain at risk of sexually transmitted infections [1,2]. There have been a number of recent outbreaks of syphilis in the UK and elsewhere [3,4,5]. Many of these outbreaks have disproportionately affected HIV-positive individuals, especially men who have sex with men [6,7], although the HIV status of many remains unknown. The management of these outbreaks has been made more complex by the frequency of anonymous sexual partners and the association of oral sex as a significant risk factor for transmission. It is known that syphilis enhances HIV transmission [8] and that syphilis can present and behave atypically in the context of HIV infection [9]. These factors suggest a need for health care workers from all specialities involved in the care of HIV positive individuals to be vigilant in their screening and management of syphilis.

1.2 The need for further guidance

There are existing UK national guidelines from the Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases) available for the management of early and late syphilis [10,11], however HIV care is provided in a number of settings outside genitourinary medicine (GUM) clinics and there are marked variations in the local implementation of existing guidelines in those who are HIV-infected. Given the recent syphilis outbreaks, the MSSVD HIV Special Interest Group has been asked to propose clinical standards for syphilis management in HIV-positive adults including during outbreak situations as part of a larger piece of work looking at the sexual health of HIV-positive individuals. It must be emphasised that this document supplements the updated Clinical Effectiveness Group (CEG) guidelines [10,11] and Public Health Laboratory Service (PHLS) sexually transmitted infection outbreak guidelines [12] and is intended to support rather than replace the guidance contained in these documents, by describing minimum standards and making these available to all those involved in HIV care.

2. Testing for syphilis in HIV-positive individuals

MINIMUM STANDARD: All HIV care providers must offer sexual risk assessment and, if appropriate, screening for sexually transmitted infections every 6 months for HIV-positive patients under follow-up. This may be within the clinic itself or by referral to appropriate colleagues.

A sexual history should be obtained and documented at least every 6 months in those being followed up for HIV. It is essential that HIV service providers consider sexual health as an integral component of routine HIV care. Obstacles that may prevent this are lack of

training or discomfort of clinic staff, insufficient facilities or lack of time during consultations [13]. Where HIV care is provided in non-GUM settings, formalised links or care pathways should be established to ensure that adequate sexual health care is integrated into patient management. Further details of this sexual health care will be proposed in the forthcoming guidance on STI screening and management in HIV positive individuals, from the MSSVD HIV Special Interest Group.

2.1 Syphilis screening as part of ongoing HIV clinical care

MINIMUM STANDARD: *All HIV-positive patients under regular follow-up should have syphilis serology documented at baseline and subsequently and 12 monthly thereafter.*

Evidence for the optimal screening interval is lacking at present and therefore this recommendation is based on expert opinion and current practice. The 12 month recommendation reflects practice in many UK HIV services and current practice elsewhere [14, 15] The Seattle service suggests that the 12 month interval is used regardless of whether a history of consistent condom use is given, as this has little effect on the STI prevalence in men who have sex with men [14] and indeed the recent syphilis outbreaks in the UK have been characterised by the high frequency of oral sex as the apparent risk factor [16].

It is recognised that a history of sexual activity may not be elicited from all HIV-positive individuals under follow-up, however the recommendation for annual serological testing is made on the basis that a full sexual history taking may not be available in the HIV clinic setting and that treponemal infection can relapse without new exposure. If a patient declines annual syphilis serology, this should be documented, with the reason, in the casenotes.

Screening can be performed in a routine situation using the syphilis EIA or the TPHA (or equivalent) combined with a reagin test (usually the VDRL or RPR). The tests must be performed in laboratories with appropriate quality accreditation.

2.2 Syphilis screening in an outbreak situation

HIV carers and associated laboratories have a sentinel role in identifying possible outbreaks. Routine local clinical surveillance procedures need to be in place. HIV carers play an important role in identifying outbreaks at an early stage and should work alongside genitourinary medicine colleagues, public health, health promotion and local voluntary sector agencies in managing the outbreak [12].

MINIMUM STANDARD: *In an outbreak situation, serological testing for syphilis should be offered to HIV-positive individuals every 3 months, to coincide with HIV follow-up attendances.*

In accordance with the Public Health Laboratory Service, a sexually transmitted infection outbreak is an overarching term which includes: observed number of cases greater than expected over a defined time period; linked cases of STIs; the need for re-organisation of services or identification of additional resources to manage cases; any case of congenitally acquired infection.

Since many of the UK outbreaks have been characterised by both the high number of anonymous contacts and the high rate of associated HIV infection, it is recommended that the HIV positive population should be considered for more frequent screening even where no contact with a case of known syphilis is reported. This recommendation is based on expert opinion rather than evidence and should be reviewed in the light of emerging information as the current epidemiology in the UK unfolds.

3. Clinical features of syphilis in HIV-positive individuals

Genital ulceration in primary syphilis can present as atypical and/or multiple ulcers, and may resemble an episode of genital herpes. Features of syphilis can easily be mistaken for clinical manifestations of HIV infection. Several cases of syphilis in the UK outbreaks have been transmitted by oro-genital sexual contact alone, therefore careful oral examination with an appropriate light source is recommended.

Features of syphilis in HIV include:

- Generalised lymphadenopathy
- Splenomegaly
- Hepatitis
- Skin rashes and/or alopecia
- Oral manifestations
- Cognitive impairment
- Meningitis
- Cranial nerve palsies
- Myelopathies
- Uveitis (commoner in HIV-positives [17])

Although open to debate, there appears to be a significant risk of neurological involvement in early syphilis in patients who are HIV-positive [9,18,19] and so it appears plausible that neurological symptoms may be more likely in the context of HIV. Therefore a high index of suspicion backed by serological testing is required to exclude syphilis.

4. Diagnosis of syphilis in HIV-positive individuals

Where lesions that are clinically suspicious of primary syphilis are identified, attempts must be made to identify treponemes by dark ground microscopy. Where HIV care is provided in a non-GUM setting, referral to an appropriate clinic to enable this is required. *Treponema pallidum* can also be demonstrated using a direct fluorescent antibody (DFA) test or by polymerase chain reaction (PCR) where available. These latter two methods may help to distinguish *T.pallidum* from commensal treponemes in oral lesions.

Existing serological tests for syphilis appear to be generally as reliable in HIV-positives compared with HIV-negatives, although there is a higher incidence of biological false positive reagin tests which may be up to 11% [20,21,22]. A false negative reagin test has also been reported [23], but it is possible in late HIV infection that some cases of syphilis are diagnosed by other means rather than serology, such as on silver stains of biopsy samples or with dark ground microscopy only.

Following a positive syphilis screen (enzyme immunoassay or treponemal plus reagin tests), all positive results should be confirmed on a second sample with supplementary tests. The Fluorescent Treponemal Antibody absorption test (FTA-abs) should be performed if early syphilis is suspected. In HIV patients, consideration should be given to a possible prozone phenomenon (especially in cerebrospinal fluid) producing a false negative result and dilutions performed.

Where serology is equivocal, this should be repeated and further management based upon the level of clinical suspicion. Re-infection or relapse of syphilis should be considered where the reagin titre increases 4-fold. For example; a rise in VDRL titre from neat to 1 in 4, or a rise from 1 in 2 to 1 in 8.

In patients where there is a history of previously treated syphilis, serology is likely to remain positive lifelong. In such situations, strenuous efforts should be made to confirm that the treatment regimen was complete and effective [10], particularly if the individual is suspected or known to have been HIV positive at the time of syphilis treatment (see treatment recommendations below).

If the individual is found to have received suboptimal therapy then re-treatment should be considered, particularly in the presence of clinical features that could be consistent with syphilis.

It is also recommended that a pregnancy test should be performed after appropriate discussion in all HIV positive women found to be infected with syphilis.

5. Treatment of syphilis in HIV positive individuals

5.1 Treatment regimens

MINIMUM STANDARD: Treatment of syphilis in HIV-positive individuals should be sufficient to produce treponemicidal levels in both serum and the CSF to prevent future neurosyphilis.

Details of recommended regimens can be found in the Clinical Effectiveness Group (CEG) guidelines for early and late syphilis (www.mssvd.org.uk).

Penicillin remains the treatment of choice.

A commonly used regimen in the UK is intramuscular Procaine penicillin G 2.0 megaunits (2,000,000 IU) once daily plus oral probenecid 500 mg x4/day for 17-21 days. This is equal to 8 ml of reconstituted Jenacillin A, which is usually given as two 4 ml injections.

Procaine penicillin G is currently available in the UK as Jenacillin A which contains both procaine and benzyl penicillin G. One vial of Jenacillin A contains 1500 mg (1.5 megaunits) of procaine penicillin G and 300mg (300,000 units) of penicillin G sodium. 4.5 ml of water for injection is added to the vial to produce 6 ml after constitution. Each ml therefore contains 250,000 units of procaine penicillin G. The dose of penicillin G sodium in Jenacillin A is ignored in the calculations.

Although this involves the administration of large volumes over an extended time period, it remains the recommended first-line therapy and strenuous efforts should be made to use this regimen wherever possible. Appropriate local systems should be established to ensure that injections can be given when clinics are shut (e.g. utilising inpatient HIV units, accident & emergency departments or other appropriate arrangements).

There have been few treatment failures in HIV-positive patients using Penicillin G (Benzylpenicillin) regimens [10]. There is a higher risk of treatment failure with Benzathine Penicillin G in HIV-positives. In an American randomised trial of early syphilis, the serological relapse rate was 18% at six months, even if the Benzathine Penicillin G was enhanced with amoxicillin plus probenecid [24]. However, Benzathine Penicillin G regimens may be valuable when adherence is in doubt, providing adequate follow up can be maintained.

By treating all stages of syphilis in HIV adequately with a CSF treponemicidal regimen, future confusion about sub-optimal therapy is avoided should the patient develop neurological or psychiatric symptoms and/or signs.

Second line regimens include oral doxycycline or oral amoxicillin with probenecid, but these are considered sub-optimal in HIV as they are not known to be fully treponemicidal in the CSF.

Ceftriaxone has been used as an alternative agent with reported good CSF penetration, but data is currently limited. There is also insufficient data to support the use of azithromycin at present. Erythromycin is not recommended because of poor CSF penetration.

5.2 Need for lumbar puncture

MINIMUM STANDARD: *All HIV-infected patients with positive syphilis serology must have a full documented neurological examination.*

If neurological symptoms or signs are present, a head scan and lumbar puncture is required to exclude other HIV related conditions. Asymptomatic HIV positive patients do not require a lumbar puncture unless they are going to be treated with a course of antibiotics where there is uncertainty about whether CSF treponemicidal levels will be achieved. Procaine penicillin is known to be treponemicidal in CSF using the regimen above.

The interpretation of CSF syphilis tests in HIV-positive individuals can be difficult even in the absence of blood contamination. Ideally, the first CSF sample should not be sent for syphilis tests owing to the risk of blood contamination.

- Mononuclear pleocytosis and elevated protein can occur in HIV without neurosyphilis [18].
- The CSF reagin test is insensitive in HIV [27].
- A negative CSF FTA-abs or MHA-TP probably excludes neurosyphilis [27,28].

It also good practice to document a full physical examination including cardiovascular examination with pulse and blood pressure readings. Further investigations such as a chest radiograph and an electrocardiogram are not routinely required in HIV-positive individuals with early syphilis. These are often performed in later disease, but the evidence for this practice is lacking.

5.3 Tests for other sexually transmitted infections

MINIMUM STANDARD: A full sexual health screen (including investigations for gonorrhoea and chlamydia) should be performed in all patients with proven or suspected syphilis.

Where HIV care is provided in a non-GUM setting, appropriate referral should be made at the earliest opportunity. Samples may be required from multiple anatomical sites to exclude co-infection.

5.4 Partner notification

Where sexual partners are traceable, strenuous attempts should be made to recommend screening of such contacts for syphilis (and other sexually transmitted infections including HIV). Provider referral should be offered as an alternative means of partner notification. If HIV care is provided in a non-GUM setting, involvement of health advisers in local genitourinary medicine services (where such procedures are routine) is recommended.

Where sexual partners are untraceable, consideration of alternative strategies for screening and outbreak control should be considered [12,16].

5.5 Follow-up

Unless there are circumstances to suggest inadequate response to initial therapy, all patients should be monitored for evidence of clinical or serological relapse at 3 monthly intervals to one year and then at least annually lifelong.

Follow-up should include the reagin titre. Relapse or reinfection should be considered if there is a 4-fold rise in the VDRL or RPR titre.

6. Management of individuals at high risk but unknown HIV status

Where an individual is unwilling or unable to have an HIV antibody test performed, but HIV is considered likely on clinical grounds, it is recommended that treatment should be administered as per individuals with proven HIV infection.

Membership of the MSSVD HIV Special Interest Group

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