Introduction
The aim of this paper is to describe the current view regarding syphilis and HIV-infection in Europe. The method used is asking key-questions and giving answers to those questions, having reviewed the data available. The concept-paper including proposed answers to key questions was discussed in the IUSTI/WHO Europe Workshop Syphilis Management at the IUSTI Europe Conference on STI, October 7-9, 2004, 19 experts participating (IUSTI Europe: 13; WHO Europe: 6; USA: 1), in addition to 4 observers. Here the final version is given, after discussion in the workshop.

Syphilis and HIV-infection share close historical, behavioural and epidemiologic patterns. It is well recognized, that syphilis is associated with both acquisition and transmission of HIV (relative risk 2-3). The epidemic of early syphilis, observed in developed countries, affects mainly MSM with an over-representation of HIV-infected persons. Close correlation is documented between the present syphilis epidemic and recent relapse into unsafe sexual behaviour, particularly in HIV-positive patients treated with HAART (also at risk for gonorrhoea and L2 chlamydia proctitis).[1]

From the emergence of HIV and AIDS and because immune suppression could alter the course of syphilis, concern has been focused upon increased severity of the disease with atypical, malignant forms, rapidly progressing towards neurosyphilis, protracted evolution and atypical serologic patterns. The reality is different.

Clinical presentation
Syphilis has been re-discovered by clinicians at the end of the last century! All the so-called atypical and malignant cases are classical and historical. Bias of publication have been obvious in HIV. In the biggest prospective multicenter study on that subject, Rolfs et al. have shown that, although there are small variations in early syphilis presentation in HIV-positive patients (more multiple chancres, more primary-secondary overlaps and more Jarisch-Herxheimer reactions),[2-4] the general aspect of early syphilis is not altered.[5]

Key question 1. Is serologic failure more frequent in HIV-positive patients after conventional treatment of early syphilis (primary, secondary and early latent syphilis acquired <1 year previously) and are there any practical implications for follow-up?
Some rare cases of secondary syphilis with non-reactive serum tests (both treponemal and non treponemal) have been observed in HIV-positive patients. A definite diagnosis can be made by dark field microscopy, second testing with dilution of serum and biopsy (to detect T. pallidum). PCR DNA detection of T. pallidum or the rabbit infectivity test can also be used. Although already described in the pre-HIV era, this situation could be more frequent in HIV.

Most of the studies do not find any statistically significant difference concerning the evolution of serologic tests for syphilis (STS) after treatment of early syphilis, according to HIV-status (see also paper nr 3 : P. French, ‘Serologic follow-up after treatment of syphilis in Europe’, key question nr 1: ‘What is the definition of an adequate serologic response after treatment of early syphilis and how often is the response inadequate according to that definition in HIV-negative and HIV-positive patients?’).[6] Treponemal tests seroreversion could be more frequent in HIV, but VDRL-RPR test evolution seems regular. Serologic treatment failure (less than fourfold decrease of initial titer of non-treponemal test) has

1 Answers to key questions are based on proposed answers, which were discussed in the workshop.
been documented as more frequent in HIV-positive patients in only 2 studies and furthermore the difference was observed only in primary syphilis at 6 months follow-up post treatment and neither in secondary or early latent syphilis nor at 1 year.[5,7]

**Answer:** The evolution of non-treponemal tests for syphilis is generally regular in HIV-positive patients after conventional treatment of early syphilis. The approach of serologic failure and retreatment should not be different from the classical approach in HIV-negative patients. Close follow-up (clinically and serologically) is warranted, whatever the HIV status (e.g. at 3, 6, 12 and 24 months).

**Key question 2.** Is CSF examination indicated in HIV-positive patients with early syphilis?

According to the European 2001 and American CDC 2002 syphilis guidelines CSF examination is not indicated before starting treatment of early syphilis (primary and secondary syphilis and early latent syphilis acquired <1 year previously). CSF abnormalities occur in about 20-30% of patients with early syphilis,[8,9] but the clinical relevance of that finding is very limited, as standard treatment for early syphilis is very effective. The risk of developing symptomatic neurosyphilis is judged to be very small for HIV-negative patients (see paper nr 2: R. Parkes and P.C. van Voorst Vader: ‘Treatment of syphilis: the European view’, key question nr 2: ‘Is benzathinebenzylpenicillin (BBP) 2.4 MU i.m. sufficiently effective in early syphilis?’).

The selection of patients in whom CSF examination will bring relevant information for optimal management, is the major issue we have to face in HIV-positive patients. Approaches differ widely among clinicians, mainly on theoretical bases. Given the high rate of CSF examination refusal, the morbidity of lumbar puncture, the difficulties in assessing the diagnosis of neurosyphilis (still more challenging because of baseline CSF pleocytosis in HIV)[10] and the low risk of evolution of early syphilis towards symptomatic neurosyphilis after conventional therapy, we do not think it is realistic to recommend CSF examination in all patients presenting with HIV and early syphilis.

Two longitudinal studies have strengthened this position, showing that CNS involvement is not more frequent in HIV-positive patients with early syphilis as compared to HIV-negative patients.[5,9] Although CSF abnormalities were observed not infrequently (increased CSF protein, CSF treponemal tests for syphilis) in HIV-positive patients with early syphilis as compared to HIV-negative patients, [5,9] the findings did not differ according to HIV-status and moreover were not correlated with clinical treatment failures.

**Answer:** CSF examination is not indicated in HIV-positive patients with early syphilis, unless there are neurologic symptoms, which may include auricular and ocular symptoms.

**Key question 3.** Should treatment for HIV-positive patients with early syphilis (primary, secondary and early latent syphilis acquired <1 year previously) be different from HIV-negative patients?

There is no study establishing, that HIV-positive patients with early syphilis should be treated differently from HIV-negative ones. We still use and recommend benzathine penicillin G (benzathine benzylpeniciliane/BBP) in early syphilis (2.4 million units i.m.), whatever the HIV status (see also paper nr 2: R. Parkes and P.C. van Voorst Vader: ‘Treatment of syphilis: the European view’, key question nr 2: ‘Is benzathinebenzylpenicillin (BBP) 2.4 MU i.m. sufficiently effective in early syphilis?’).

**Answer:** Given the generally regular aspect of early syphilis (both clinical and serologic) in HIV-positive patients, standard treatment (BBP 2.4 MU i.m.) need not be different from HIV-negative patients.

**Key question 4.** Should cerebrospinal fluid (CSF) examination be performed in HIV-positive patients with late latent syphilis or latent syphilis of unknown duration?

A recent prospective multicentre study again raises the dilemma on the usefulness of CSF examination, both in HIV-positive and HIV-negative patients, before starting treatment of patients with late latent syphilis or latent syphilis of unknown duration.[11] Neurosyphilis was more likely to occur, if the serum-RPR test titre was ≥ 1 : 32 (OR: 6 in HIV-positive and 11 in HIV-negative patients), if CD4+ cell count was < 350 (OR: 3) and if both criteria were present (OR: 19). Although this study is the best one on the subject, it should be interpreted with caution. Most of the patients, who had CSF examination, were in the late latent stage, but some had early syphilis (in which clinically non-relevant CSF abnormalities do not infrequently occur), with over-representation of HIV and individuals meeting CDC criteria of 1993 for late latent syphilis. The study tends to demonstrate a higher risk of neurosyphilis in early stages with high RPR test titres, but one wonders if a laboratory finding consistent with neurosyphilis (CSF-VDRL test reactive) is of clinical significance in early syphilis and in all cases of latent syphilis of unknown duration (some of these cases are bound to have early latent syphilis). CSF invasion by *T. pallidum* is known to occur early in the course of the disease,[9] asymptomatic meningitis is classical during the secondary phase and apparently does not have the same significance as late parenchymal CNS involvement. And although CSF-VDRL test reactivity remains the gold standard in the USA for the definition of neurosyphilis (see paper nr 5: B.L. Schmidt, ‘Laboratory diagnosis of neurosyphilis in Europe’), its
specificity in demonstrating (asymptomatic) neurosyphilis in latent syphilis of unknown duration could be lower than in late symptomatic neurosyphilis. Older publications have demonstrated, that not only may CSF-VDRL test reactivity be observed in 20% of early syphilis,[12] but CSF-VDRL test reactivity also parallels serum-RPR test reactivity in syphilis (given a non traumatic puncture).[13]

The main problem, when discussing the issue whether one should recommend CSF examination in HIV-positive patients with late latent syphilis or latent syphilis of unknown duration, is that robust prognostic data on the risk of developing symptomatic neurosyphilis from asymptomatic neurosyphilis after standard parenteral treatment of late latent syphilis are lacking (see also: a) paper nr 2: R. Parkes and P.C. van Voorst Vader: ‘‘Treatment of syphilis: the European view’’, key question nr 3: ‘‘Is benzathinepenicillin (BBP) 2.4 MU i.m. on day 1, 8 and 15 sufficiently effective in late latent syphilis and is there an indication for CSF examination in HIV-infected patients with late latent syphilis or latent syphilis of unknown duration before treatment?’’; b) paper nr 3: P. French, ‘‘Serologic follow-up after treatment of syphilis in Europe’’, key question nr 5: ‘‘How should HIV-negative and HIV-positive individuals with an inadequate serologic response after treatment of late latent syphilis be managed?’’). The risk of asymptomatic neurosyphilis as diagnosed by a positive CSF-VDRL test and elevated WBC count in CSF appears to be increased in HIV-infected patients with immune impairment and normalization of CSF abnormalities could be slower after neurosyphilis therapy.[11] But does this result in a risk of developing symptomatic neurosyphilis despite standard treatment with BBP i.m. for late latent syphilis of such magnitude, that standard CSF examination before treatment should be recommended? The picture is far from being complete. And one should be aware of circular reasoning.

Risk factors as high non-treponenemal test titer and CD4+ cell count may prove to be of value in deciding which patients are at increased risk of asymptomatic neurosyphilis and should be given i.v. penicillin. It may be possible to roughly estimate the risk of developing symptomatic neurosyphilis from asymptomatic neurosyphilis, which depends on the degree of CSF abnormalities,[14,15] but prospective studies with present-day tests are needed. A quantitative serum TPAb test may help, as a serum TPAb titer <1:640 (which might be a TPPAb titer of <1:640 or <1:1280) makes (asymptomatic) neurosyphilis unlikely, thus argues against CSF examination (see paper nr 5: B.L.Schmidt, ‘‘Laboratory diagnosis of neurosyphilis in Europe’’). Conventional treatment as for late latent syphilis (having excluded clinically symptomatic neurosyphilis, including auricular and ocular syphilis) with BBP 2.4 MU i.m. on day 1, 8 and 15 and careful clinical and serologic follow-up during e.g. 2 years plus instruction of the patient when to contact the physician, remains the alternative option.

Answer: There are two options for HIV-positive patients with late latent syphilis or latent syphilis of unknown duration, having clinically excluded neurosyphilis, including auricular and ocular syphilis:
1) CSF examination in all patients (use of criteria as non-treponenemal serum test titre and CD4+ cell count needs confirmation) and treat with intravenous penicillin if asymptomatic neurosyphilis is documented;
2) conventional treatment with BBP 2.4 MU i.m. on day 1, 8 and 15 in combination with clinical and serologic follow-up during e.g. 2 years and instruction of the patient when to contact the physician. Prospective studies are needed to facilitate future recommendations for optimal management of these patients.

Key question 5. What are the alternative options for treatment of syphilis in HIV-positive patients suspected of a penicillin allergy?

Regarding alternatives for penicillin (see also paper nr 2: R. Parkes and P.C. van Voorst Vader, ‘‘Treatment of syphilis: the European view’’, key question nr 4: ‘‘Penicillin allergy: what are the alternatives?’’), our clinic does not recommend tetracyclines in HIV-positive patients allergic to penicillin, because to our knowledge no study has been conducted in HIV-positive patients. We observed several clinical failures in HIV-positive patients with secondary syphilis treated with doxycycline. Penicillin desensitization is an important option, which we use frequently (desensitization and first treatment dose all in one day), mostly in patients with late latent syphilis, after allergy tests.
Azithromycin should not be recommended, because of treatment failures both in HIV-positive and HIV-negative patients due to macrolide resistance.[16]

Finally, although ceftriaxone has been used with success in patients with early and latent syphilis and also neurosyphilis,[17,18] and could be useful in patients allergic for penicillin (but not in patients with anaphylaxis), we are reluctant to use it. First because of the risk of allergic cross-reactions, second because penicillin desensitization is simple and easy and third because we think the multiple injections and the cost compare unfavourably with either benzathinepenicillin G (early and latent syphilis) or penicillin G infusion (neurosyphilis).

Answer: As alternative for penicillin treatment of HIV-positive patients with syphilis and penicillin allergy azithromycin is not recommended (drug resistance). Caution is recommended with doxycycline (clinical failures observed in secondary syphilis) and ceftriaxone (multiple injections and cost compare
unfavourably with i.m. BBP and i.v. penicillin). Penicillin desensitization for anaphylaxis, after allergy tests, is an important option, which is simple to perform.

References