Serologic follow-up after treatment for syphilis in Europe (paper nr 3)

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Introduction
The aim of this paper is to describe the current view regarding serologic follow-up after treatment of syphilis 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.

The following terminology is used to describe serological responses: seroconversion (test becomes positive), seroreversion/seronegativation (test becomes negative), seroresistance (no fourfold titre decline), serofast (test remains positive at a low titre after adequate initial response). In the literature the term seroconversion is occasionally also used for seroreversion/seronegativation and the term serofast (and also the term seroresistance) is often used for a persistently stable low titer (often not known whether there ever was an adequate initial response).

Key question 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?

The definition differs amongst the major STI treatment guidelines. There is general acceptance, that a fourfold reduction in titer (decrease of two dilution steps) of a non-treponemal test (RPR and/or VDRL test) after treatment of early syphilis should be expected. But there is variation in the guidelines over the speed in which this should be achieved and the impact of HIV infection. An important requirement for reliable monitoring of follow-up titers of a non-treponemal test is, that follow-up serology is performed at the same laboratory, using the same test equipment as for the initial test, because there appears to be only about 70% agreement between different test sites. Also the follow-up serology titer should preferably be compared with the titer at the day of treatment, as the titer may have increased (or decreased if false positive) since the last test previous to treatment.

The European syphilis guideline 2001 suggests, that after treatment of early syphilis (primary/secondary and early latent syphilis acquired <1 year previously) a fourfold decrease in titer (a two step dilution decrease) of non-treponemal tests should be expected by 6 months for HIV-negative individuals, in accordance with the American CDC guidelines 1998 and 2002, and by 12 months for those with HIV-infection.[1] They also state that the exact value of the serum titer response of non-treponemal tests has never been fully elucidated and that universally accepted standards for cure or failure using the serologic response do not exist.

The UK syphilis guideline 2002 states, that a fourfold or greater decline of the titer of a non-treponemal test should be observed within 3-6 months after treatment of early syphilis (primary, secondary and early latent syphilis acquired <2 years previously). They add, that the patient may be

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1 Answers to key questions are based on proposed answers, which were discussed in the workshop.
discharged, if the patient remains asymptomatic and the VDRL/RPR test is negative or serofast at one year.[2]

The Russian Federation syphilis guideline 1999, incorporated as an appendix in the European syphilis guideline of 2001 and in the 2003 WHO Europe review on management of syphilis infected patients in the Russian Federation,[1,3] suggests, that patients adequately treated for early syphilis (primary/secondary and early latent syphilis acquired <2 years previously) should be considered to have an inadequate response, if they have a stable positive RPR or VDRL test >1 year after treatment (seroresistance) or if an at least fourfold decline of the titer of these tests occurs ≥1 year after treatment without further decrease in titer (delayed response).

The American CDC syphilis guideline 2002 states,[4] that: a) definitive criteria for cure or failure have not been established; b) a non-treponemal tests titer may decline more slowly for patients who previously had syphilis; c) treatment failure usually cannot be reliably distinguished from reinfection; d) a recent trial demonstrated, that 15% of patients with early syphilis treated with the recommended therapy will not achieve a two dilution decline in a non-treponemal test titer at 1 year following treatment (no reference is given, but probably the study of Rolfs et al is referred to, published in 1997 and reviewed in 1999)[5,6]; e) failure of non-treponemal test titers to decline fourfold within 6 months after treatment of primary and secondary syphilis is indicative of probable treatment failure. This guideline does not give criteria for the expected serologic response after treatment of early latent syphilis, for which the recommended treatment is the same as for primary and secondary syphilis.

A number of studies suggest, that the great majority of individuals receiving adequate treatment for early syphilis achieve a negative VDRL/RPR test by 24 months. In the pre-HIV era Brown et al., in a reanalysis published in 1985 of an earlier study reported in 1972, suggested, that an adequate response to treatment (fourfold decrease of VDRL test titer) should be observed by 3 months in most adequately treated individuals with early syphilis.[7] This reanalysis reported, that the VDRL test titer fell more slowly than the 95th percentile in 7% of cases treated with BBP 2.4 MU i.m., in 46% of those reinfected and in 89% of those with clinical failure after treatment.[7,8]

Fiumara reported, that all adequately treated individuals should have a negative VDRL test by 12 months after primary syphilis and by 24 months after secondary and early latent syphilis.[9-11] However, higher doses than BBP 2.4 MU i.m. were given in these three studies and the results do not agree with other less optimistic studies. These studies were also not included in the 1995 review by Rolfs, because of serious methodological flaws and important differences in analytical methods.[12]

Talwar et al., in a study of 1532 cases treated in India from 1976-1981,[13] reported that seroreversion of the VDRL test after treatment of early syphilis with BBP 2.4 MU i.m. is not a universal occurrence. Six months after treatment the VDRL test was still reactive in 16% of primary syphilis, 28% of secondary syphilis and 19% of early latent cases (syphilis acquired <2 years previously). After 12 months these percentages were 11%, 17% and 16%, at 30 months 7%, 8% and 12%. Higher doses of treatment (BBP 4.8 MU i.m. and procaine penicillin instead of BBP) accelerated the speed of seroreversion.

Romanowski et al reported in a study of 882 cases treated in Canada from 1981-1987 with BBP 2.4 MU i.m., that 72% of primary syphilis and 56% of secondary syphilis cases had seroreverted (to negative) in the RPR test by 36 months.[14] This is a lower percentage of seroreversion than reported with the VDRL test.[7,13] Using the criterion of a fourfold titer decline serologic treatment failure was observed by Romanowski et al at 6 months in 15-23% of primary and secondary syphilis.[6,12,14]

Augenbraun and Rolfs state, on the basis of the study of Rolfs published in 1997,[5] that approximately 15% of patients with early syphilis (primary, secondary and early latent syphilis acquired <1 year previously) fail to meet the criterion of a fourfold titer decline by as late as 12 months.[6] In the study of Romanowski et al a delayed titer decline was observed in early latent syphilis (acquired <1 year previously) as compared to primary and secondary syphilis, a fourfold titer decline being observed not at 6 but at 12 months.[14] The data of Brown et al.[7] and Romanowski et al.[14] lead Rolfs to state, that, given the rarity of clinical failure, the positive predictive value of a 4-fold decline of a non-treponemal test titer at 6 months in non-HIV-infected individuals is probably very low.[6,12]

Regarding the influence of HIV infection on the serologic response of treatment of early syphilis, conflicting findings have been reported (see also paper nr 4: M. Janier, “Syphilis and HIV-infection: the European view”). Some controlled studies suggest, that the serologic response to adequate treatment of early syphilis is similar amongst individuals with or without HIV infection.[15,16,17] other controlled studies however reported that this is not the case.[5,18,19,20]

Reporting a normal serologic response in HIV-infected patients, the study of Gourevich et al. involved early syphilis in 14 HIV-infected and 5 HIV-negative cases and defined an adequate response
as a fourfold decrease of RPR test titer <3 months after standard treatment of primary and secondary syphilis and <6 months after standard of early latent syphilis, standard treatment being BBP 2.4 MU i.m.[15] The prospective study of Goeman et al. involved 47 HIV-positive and 73 HIV-negative female cases including early (latent) syphilis cases and late latent syphilis cases.[16] All were treated with BBP 2.4 MU i.m. at day 1, 8 and 15 and 83% of HIV-positive patients and 90% of HIV-negative patients reached at least a fourfold decline of RPR test titer 2 years after treatment. The prospective study of Janier involved patients with primary (17 HIV-positive, 25 HIV-negative) and secondary syphilis (33 HIV-positive, 11 HIV-negative) and latent syphilis (19 HIV-positive, 13 HIV-negative).[17] The decrease of VDRL test titer was not different between HIV-negative and HIV-positive cases. Seroreversion of the VDRL test was not related to baseline CD4+ cell count.

Reporting an abnormal serologic response in HIV-infected patients, Telzak et al. in a retrospective study observed a delayed serologic response in primary syphilis cases, i.e. a fourfold or greater decrease of the RPR test titer in 15/28 (53%) HIV-infected cases and 153/210 (73%) HIV-negative cases at 6 months after treatment of primary syphilis, whereas there was no significant difference when comparing the serologic response in secondary syphilis, although this group also showed a (non-significant) trend towards a delayed response.[18] Yinnon et al. also reported a delayed RPR test titer response in a retrospective study of 64 HIV-positive cases and 64 HIV-negative controls, but the data at 6 months after treatment for the early syphilis cases (n=26 in each group) are not convincing.[19] Marra et al. reported a delayed serum VDRL titer response in 12 HIV-infected cases as compared to 8 HIV-negative cases in a group of 22 patients, 8/22 having early syphilis, of whom 6 were HIV-positive.[20] Rolfs et al. studied 541 cases with early syphilis, including 101 HIV-infected cases.[5] They were given either a single dose of BBP (2.4 million units IM) or this regime plus amoxicillin and probenecid (2 gram amoxicillin and 500 mg probenecid orally 3x daily for 10 days).

In the primary stage the HIV-positive cases had a significantly higher risk of serologic failure, as tested by the RPR test at 6 months, than the HIV-negative cases (22% vs. 5%) and in secondary syphilis the risk was increased (23% vs. 10%), but this difference was not statistically significant. For early latent syphilis this trend was reversed: the percentages were 19% vs. 35% for HIV-infected and HIV-negative cases. Multivariate analysis of the mean decrease of RPR test titer indicated, that the titer decreased more slowly among HIV-infected cases. Only one case (in the HIV positive group) had clinically defined treatment failure. The rates of serological treatment failure were similar between HIV-infected cases with a CD4+ percentage of <14% and ≥14%.

The latest review on syphilis and HIV infection, published in 2004, states that HIV-infected patients with early syphilis may have higher rates of treatment failure, adding that clinical failure is uncommon and serological failure is not.[21]

Answer: An adequate serologic response after adequate treatment of early syphilis (primary and secondary syphilis and early latent syphilis acquired <1 year previously) is defined by the European 2001 and American 2002 syphilis guideline as a fourfold titer decline of a non-treponemal test (generally VDRL or RPR test) at 6 months. However, a substantial percentage (about 15%) of HIV-negative patients do not meet that criterion. In HIV-positive patients that percentage may be higher, although data are conflicting. Given the rarity of clinical failure after standard treatment of early syphilis in HIV-negative as well as HIV-positive patients, the positive predictive value of a 4-fold titer decline of a non-treponemal test at 6 months appears to be low. This will also apply to the more strict criteria recommended in the 2001 syphilis guideline of the Russian Federation.

An important requirement for reliable interpretation of follow-up test results of a non-treponemal titer monitoring test is, that follow-up serology is performed at the same laboratory, using the same test equipment as for the initial test. Also the follow-up serology titer should preferably be compared with the titer at the day of treatment, as the titer may have increased (or decreased if false positive) since the last test previous to treatment.

Key question 2. What is the definition of an adequate serologic response after treatment of late latent syphilis?

There are few evidence-based recommendations on this issue. None are found in recent European (2001), American (2002) or UK (2002) syphilis guidelines.[1,4,22] The Russian Federation syphilis guideline 1999 requires normalization of reaginic reactions.[1,3] It is known, that late latent syphilis patients often have a persistent positive non-treponemal test at a low titer (serofast), that does not decrease in titer after treatment. Fiumara observed that 56% of 209 patients with late latent syphilis remained positive in a non-treponemal test 5 years after treatment.[23] Gourevich et al. stated, that an adequate response for patients with late latent syphilis is any decrease in RPR test titer if initially ≥1:32 or absence of an increase in RPR test titer if initially <1:32, which is cited from the American CDC
Inadequate or impossible to monitor as in latent syphilis, one might decide in favour of additional treatment. If the clinical response was adequate, one might decide against additional treatment. If the clinical response was (primary, secondary and early latent syphilis acquired <1 year prior to treatment) has been adequate, one might decide against additional treatment. If the clinical response was inadequate after standard treatment (with BBP 2.4 MU i.m.) of early syphilis patients had a fourfold decrease of a non-treponemal test titer at 12 months.[24]

It is generally assumed, that follow-up of patients with serofast serology (continued stable low-titre non-treponemal test serology) is not strictly indicated, provided instruction is given when to contact the physician. Answer: No definition of an adequate serologic response after adequate treatment of late latent syphilis is mentioned in currently available syphilis guidelines and data are scarce. A pragmatic approach may be to suggest the following definition of an adequate serologic response: any decrease at 1 year after treatment, preferably a fourfold decrease, of a non-treponemal test titer if initially ≥1:32 or absence of an increase in a non-treponemal test titer if initially <1:32 (the titer should at least remain serofast).

Key question 3. What is the evidence that an inadequate serologic response after treatment of early and late syphilis denotes persistent infection and clinical failure?

There is good evidence that failure of the serologic response is rarely associated with failure of the clinical response, i.e. identifies patients at risk for progressive disease (see key question nr 1 and 2).[6] The latest review on syphilis and HIV infection, published in 2004, states that HIV-infected patients with early syphilis may have higher rates of treatment failure, adding that clinical failure is uncommon and serological failure is not.[21] Moreover, failure of the serologic response can be difficult to differentiate from reinfection (biologically false positive reactions may also be a problem). The presence, as demonstrated by PCR and/or rabbit infectivity test, of T. pallidum in the CSF after adequate treatment does not appear to be associated with an increased risk of neurosyphilis.[5] The role of the immune system in containing a syphilitic infection has been repeatedly and extensively described.[8,12]

Answer: There is no robust evidence, that an inadequate serologic response after treatment of early and late syphilis denotes persistent infection and clinical failure.

Key question 4. How should HIV-negative and HIV-positive individuals with an inadequate serologic response after treatment of early syphilis be managed?

The suggested approach varies between the guidelines and is different for early syphilis and late latent syphilis. Regarding an inadequate serologic response after treatment of early syphilis (primary and secondary syphilis) the American CDC syphilis guideline 2002 states,[4] that: a) optimal management of these patients is not clear; at a minimum they should have additional clinical and serologic follow-up (HIV-infected patients should be evaluated at 3-months instead of 6-months intervals) and persons for whom titers remain serofast, should be retested for HIV infection; b) if additional follow-up cannot be ensured, re-treatment is recommended. This guideline also states, that some specialists recommend CSF examination, because serologic treatment failure may be the result of or be associated with neurosyphilis. When patients are re-treated, most American CDC syphilis experts recommend BBP 2.4 MU i.m. at day 1, 8 and 15, unless CSF examination indicates (asymptomatic) neurosyphilis (“in rare instances serologic titers do not decline despite negative CSF examination and repeated treatment courses; additional treatment or repeated CSF examinations are probably not warranted in these circumstances”). The American CDC syphilis guideline 2002 does not clearly state the follow-up protocol of early latent syphilis, for which the recommended treatment is the same as for primary and secondary syphilis.

The European syphilis guideline 2001 questions the recommendation of the American guideline for additional clinical and serologic follow-up or, if additional clinical and serologic follow-up is not possible, re-treatment with BBP 2.4 MU i.m. at day 1, 8 and 15 of those patients, who do not have an adequate serologic response after standard treatment (with BBP 2.4 MU i.m.) of early syphilis (primary, secondary and early latent syphilis acquired <1 year previously).[1] “If the clinical response has been adequate, one might decide against additional treatment. If the clinical response was inadequate or impossible to monitor as in latent syphilis, one might decide in favour of additional...
treatment. An increase of ≥2 dilution steps (≥4-fold titer increase) of a non-treponemal test suggests reinfection or reactivation.”[1]

The Russian Federation syphilis guideline 1999 recommends, that patients, who do not have an adequate serologic response after treatment of early syphilis (primary/secondary and early latent syphilis acquired ≤2 years previously) as defined earlier, be retreated with BBP 2.4 MU i.m. at day 1, 8 and 15 or ceftriaxone 1000 mg i.m. daily for 10 days or procaine penicillin or benzylpenicillin sodium salt during 20 days.[1,3] CSF examination is not recommended.

An important issue is, that one should consider additional tests to exclude the factor of an acute or chronic false-positive non-treponemal test (e.g. infection with HIV, HBV or HCV, auto-immune diseases like lupus erythematosus and immunomodulating medication), which may explain the inadequate serologic response. This issue appears more important, than considering the possibility, that an inadequate serological response might be the result of unrecognized neurosyphilis, as mentioned in the American CDC syphilis guideline 2002.[4,25]

Answer: As there is little evidence to suggest, that lack of a fourfold decline of the titer of a non-treponemal test at 6 months is associated with clinical treatment failure, re-treatment of adequately treated early syphilis (primary, secondary and early latent syphilis acquired ≤1 year previously) is difficult to justify in that situation, provided clinical symptoms are absent and re-infection is excluded. Such patients, HIV-negative or -positive, should be followed carefully until 12-24 months after treatment, depending on the course of the serologic response, but exclusion of the factor “false-positive non-treponemal test” should also be considered.

Key question 5. How should HIV-negative and HIV-positive individuals with an inadequate serologic response after treatment of late latent syphilis be managed?

The American CDC syphilis guideline 2002 recommends prompt CSF examination for HIV-infected patients with late latent syphilis or latent syphilis of unknown duration.[4] This guideline adds, that some American specialists recommend CSF examination of all (HIV-negative or -positive) latent syphilis patients with a non-treponemal test (RPR) titre of ≥1:32, although past data may argue against this recommendation.[6,25] It is noted, that the risk of (asymptomatic?) neurosyphilis in this situation is unknown,[4] but may be increased.[6] This guideline also recommends,[4] that if after treatment of (late) syphilis an initially high non-treponemal test titre (≥1:32) fails to decline at least fourfold within 12-24 months, patients with normal CSF should be retreated, which is regarded as reasonable practice, but for which there is no evidence, however.[6] These recommendations do not mention the issue is, that, before additional treatment is given, one might first consider additional tests to exclude the factor of a false-positive non-treponemal test (e.g. infection with HIV, HBV or HCV, auto-immune diseases like lupus erythematosus and immunomodulating medication), which may explain the inadequate serologic response.

For treatment of HIV-infected patients with asymptomatic neurosyphilis i.v. penicillin is advocated on a theoretical basis, with procaine penicillin i.m. plus oral probenecid, ceftriaxone i.m. or i.v. and oral doxycycline as alternatives, i.e. the same options as for symptomatic neurosyphilis.[1,4,6,22] Whether additional treatment with one dose of BBP 2.4 MU i.m. should be given after 14 days of treatment, as given as option in the American CDC guidelines, is unknown.[4,25] Ocular syphilis, often associated with (asymptomatic) neurosyphilis,[26] and certainly auricular syphilis (“sudden deafness” associated with syphilis), which is less frequently associated with CSF-abnormalities consistent with neurosyphilis,[8] which may occur in early syphilis and otherwise asymptomatic patients with syphilis of unknown duration, should preferentially be treated by i.v. penicillin to ensure optimal tissue penetration.[1,4]

Rompolo states in her 2004 review on syphilis and HIV, that CSF examination should be performed in HIV-infected patients with late latent syphilis or latent syphilis of unknown duration.[21] This recommendation is also given in the European (2001) and UK (2002) syphilis guidelines.[1,22] The rationale for this recommendation is not stated.

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 probable late latent syphilis or latent syphilis of unknown duration, with a serum RPR test titer ≥1:32 and a peripheral blood CD4+ cell count <350 cells/μl as risk actors,[27] but it is not generally accepted, that this should lead to standard CSF examination in these patients without neurological symptoms. In this situation a quantitative serum TPHA may help, as a serum TPHA titer <1:640 (which might be a TPPA 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”).
The risk of development of symptomatic neurosyphilis from asymptomatic neurosyphilis after standard treatment with BBP 2.4 MU i.m. on day 1, 8 and 15 (or an alternative treatment course) of late latent syphilis or latent syphilis of unknown duration is judged to be very small in HIV-negative patients and is not known in HIV-positive patients.[6,12]

Regarding the role of CSF examination in HIV-negative and especially in HIV-positive late latent syphilis patients without neurological symptoms, see also paper nr 2 (R. Parkes and P.C. van Voorst Vader, “Treatment of syphilis in Europe”) and paper nr 4 (M. Janier, “Syphilis and HIV-infection, the European view”).

Answer: There is no robust evidence to support recommendation for CSF-examination or retreatment of HIV-negative or -positive asymptomatic patients with late latent syphilis or syphilis of unknown duration (with or without asymptomatic neurosyphilis) after adequate standard treatment with BBP 2,4 MU on day 1, 8 and 15, who initially showed a high non-treponemal test titre (≥1:32), which failed to decline at least fourfold within 12-24 months. Additional tests to exclude the factor of a false-positive non-treponemal test should be considered during this period.

Patients showing a high initial non-treponemal test titre (≥1:32) with an inadequate, unexplained serologic treatment response should have careful clinical and serologic follow during at least 2 years, especially if HIV-infected. A serum TPHA titer <1:640 (which might be a TPPA titer of <1:640 or <1:1280) makes (asymptomatic) neurosyphilis unlikely, thus argues against CSF examination.

Key question 6. Which serologic follow-up scheme should be followed after treatment of early syphilis and late latent syphilis or latent syphilis of unknown duration and when should follow-up cease?

A. Early syphilis:
- European syphilis guideline 2001.[1] Recommended follow-up: a) HIV-negative patients: monthly during the first three months, then at 6 and 12 months; b) HIV-infected patients: more frequently, e.g. at 1, 2, 3, 6, 9, 12, 18 and 24 months.
- Russian Federation syphilis guideline 1999.[1,3] The duration of clinical and serologic follow up is individual, depending on treatment results. Prerequisites for cure: a) administration of adequate treatment; b) normalization of clinical symptoms; c) normalization of serologic reaginic reactions and other relevant laboratory tests. Removal of a patient from the follow-up register requires final complete serologic testing.
- American CDC syphilis guideline 2002.[4] Recommended follow-up: a) Clinical and serologic re-examination at 6 and 12 months (more frequent evaluation may be prudent if follow-up is uncertain); b) HIV-infected patients should be evaluated more frequently, i.e. at 3 months intervals instead of 6-months intervals.

Given the contradictory evidence for the influence of HIV-infection on the serologic response, there is no convincing evidence that one should intensify follow-up of HIV-infected individuals as compared to HIV-negative individuals, as advocated in the European (2001) as well as the American (2002) guidelines.

Good clinical practice might be, for HIV-negative as well as HIV-positive individuals:
- clinical follow-up at 1 month, especially if the patient was clinically symptomatic when treatment was given, but also in early latent syphilis cases (to discuss health promotion and partner notification again and also HIV-testing and other relevant subjects (e.g. emotional impact/prognosis), if necessary); alternative option for asymptomatic patients: contact at 1 month by phone or internet/e-mail;
- serologic follow-up at 3 and 6 months;
- if a fourfold decline of test titer or negativation is not observed at 6 months, one should consider to continue follow-up at 9 and 12 months, especially in HIV-infected patients and then stop, if the patient was shown to have become serofast or did show negativation, provided clinical symptoms are absent. If a fourfold decline of test titer has not occurred at 12 months, one should consider continuation of follow-up at 18 and 24 months.

Can follow-up really be stopped safely in HIV-infected patients at 12 months? The risk of development of complications (neurosyphilis) and clinical relapse appears to be small (see text above). One might consider informing the patient, that he/she is at small risk of complications and relapse and should contact the physician when in doubt about this.
B. Late latent syphilis or latent syphilis of unknown duration:
- European syphilis guideline 2001.[1] In non-HIV-infected late latent syphilis patients with a reactive non-treponemal test, which remains stable in the lowest titer range, follow-up after treatment is generally not indicated.
- Russian Federation syphilis guideline 1999,[1,3] As in these patients the Wassermann reactions often remain positive, obligatory clinical and serological control during 3 years is stipulated, every 6 months in the 2nd and 3rd year. Removal from registration or continuation of follow-up is decided individually. See ad A (early syphilis) for prerequisites for cure. Removal of a patient from the register requires: a) Final complete serologic testing, including, after neurosyphilis, CSF examination; b) Specialist examination of organs previously involved with late syphilis, including (early) visceral syphilis and neurosyphilis.
- American CDC syphilis guideline 2002.[4] A quantitative non-treponemal serologic test should be repeated at 6, 12 and 24 months.

It is suggested in this paper that serologic follow-up of late latent syphilis or latent syphilis of unknown duration may be discontinued, if:
1. any decrease at 1 year after treatment, preferably a fourfold decrease, of a non-treponemal test titer, if that titer initially was in the ≥1:32 range, has occurred and been confirmed;
2. absence of an increase of a non-treponemal test titer, if that titer initially was in the <1:32 range (the titer should at least remain serofast), has been observed;
3. seronegativation has occurred.

There is no robust evidence to recommend continuation of follow-up of HIV-positive or HIV-negative individuals with serofast serology, i.e., continued stable low-titre non-treponemal test serology, provided instruction is given when to contact the physician (see key question 2).

Answer: Relatively simple follow-up schemes for early syphilis and late latent syphilis/latent syphilis of unknown duration are suggested, combining elements of the European and American approach, taking into account feasibility and patient acceptance.

Key question 7. Does serologic follow-up after treatment of early syphilis have an important role in the control of syphilis at a population level?
Persons infected with syphilis should be tested for HIV-infection, repeatedly, if indicated, on an individual basis, because of the window-phase or continued risk behaviour.[1,4,21] All HIV-infected persons should be tested for syphilis, if indicated on a yearly basis or more frequently as indicated individually by ongoing risk behaviour.[21]

There is good evidence, that standard treatment for syphilis with penicillin based regimens (benzathine or procaine) cures almost all individuals with early syphilis. Individuals with early syphilis ideally obtain further serologic assessment to establish their post-treatment VDRL/RPR test titre response, which may also have a positive emotional effect. Serologic follow-up may also be important epidemiologically, because individual syphilis patients may be at risk for re-infection with syphilis (prevention of risk-behaviour/repeated counselling) and acquiring other STIs,[21] but serological follow-up will reveal an entirely adequate serologic treatment response in the majority of individuals.

Availability of resources is relevant for realisation of serologic follow-up. In a resource-poor setting these resources may be more usefully used for treatment of as many patients as possible, than for follow-up tests.

Answer: Depending on available resources syphilis control programmes may consider, that the identification and treatment of individuals with syphilis should have a greater priority than the long term serological follow-up of individuals, who have already received adequate treatment.

Key question nr 8. What are the serologic criteria for re-infection and are they reliable?
Guidelines generally state that a fourfold increase of a non-treponemal test titer suggests re-infection.[1,4] This increase should be sustained. One should be wary, however, of an acute or chronic false-positive non-treponemal test reaction (caused by e.g. infection with HIV, HBV or HCV, autoimmune diseases like lupus erythematosus and immunomodulating medication). Future developments may possibly offer other serologic test options as additional serologic criteria for re-infection.
Answer: It is generally assumed that a sustained fourfold increase of a non-treponemal test titer suggests re-infection. One should be wary, however, of a false-positive non-treponemal test reaction, which problem may be limited by future additional serologic criteria for re-infection.

References