Laboratory diagnosis of neurosyphilis in Europe (paper nr 5)

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Introduction
The aim of this paper is to describe the current view regarding the laboratory diagnosis 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 on 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.

Neurosyphilis is primarily a disease, which is defined by clinical symptoms, although it can be difficult to prove, that neurosyphilis is the cause of the clinical symptoms of the individual patient. Certainly in cases without neurological signs of the disease CSF examination is essential for the diagnosis. As in many other neurological diseases it is difficult to get control patients (healthy controls?) for CSF examination. Many laboratory parameters have been shown to have a high sensitivity in neurosyphilis, however, specificity wasn’t determined. In practice, the differentiation between late latent syphilis and late asymptomatic neurosyphilis is difficult.

At this workshop new data (clinical and serologic evaluation of 114 patients with neurosyphilis, i.e. 87 symptomatic and 27 asymptomatic neurosyphilis patients, of 204 patients with late latent disease, of 81 patients with early latent syphilis and of 62 with symptomatic early syphilis, a total of 461 patients), acquired since the publication in 2001,[4] will be used in order to help answer the key questions.

Recent treatment guidelines containing recommendation on laboratory diagnosis of neurosyphilis

Recent important publication on laboratory diagnosis of neurosyphilis in USA

Main published reference on laboratory diagnosis of neurosyphilis in Europe

Albumin quotient/ratio, IgG ratio, IgG index, TPHA Vienna 2000 index: definitions
- Albumin ratio/quotient: CSF / serum level of albumin, parameter for blood-brain-barrier (BBB) function
- IgG ratio: CSF / serum level of IgG
- IgG index: CSF / serum level of IgG x albumen ratio, parameter for intrathecal IgG synthesis
- TPHA index Vienna 2000: CSF TPPA titer / albumin quotient (x 1000), parameter for intrathecal synthesis of anti-T. pallidum-specific IgG

1 Answers to key questions are based on proposed answers, which were discussed in the workshop. New data, acquired since 2001 by Schmidt et al in Vienna, were presented in the workshop and have been referred to in this article, but have not been properly published.
A. Laboratory diagnosis of neurosyphilis (examination of cerebrospinal fluid (CSF)): recommendations of the American CDC STD guidelines, ed. 2002,[1]

a) CSF-VDRL test (if positive, in the absence of blood contamination: definite neurosyphilis; however: the CSF-VDRL test may be negative when neurosyphilis is present);
b) CSF FTA-absorption test (according to some experts a negative test excludes neurosyphilis);
c) CSF leukocyte count is usually elevated in neurosyphilis (>5 WBC/mm³);
d) CSF protein level.


• Lumbar puncture for examination of cerebrospinal fluid (CSF) is indicated in patients with:
  - clinical neurological symptoms possibly caused by neurosyphilis
• Lumbar puncture for examination of cerebrospinal fluid (CSF) should be considered in patients with:
  - clinical symptoms possibly caused by ocular or auricular syphilis
  - clinical symptoms possibly caused by cardiovascular or gummatous syphilis
  - concomitant HIV infection*

* For non-HIV-infected patients with late latent syphilis or latent syphilis of unknown duration CSF examination is an option. This examination is intended to exclude asymptomatic neurosyphilis, although the benefit may be marginal and the need minimal, as the risk of developing symptomatic neurosyphilis after standard parenteral treatment appears to be small in such patients.

For management of HIV-positive patients with late latent syphilis or latent syphilis of unknown duration there are two options at present (anno 2004; see paper nr 4: M.Janier, “Syphilis and HIV-infection: the European view”, key question 4: “Should cerebrospinal fluid (CSF) examination be performed in HIV-positive patients with late latent syphilis or latent syphilis of unknown duration?”; and paper nr 3: R.Parkes and P.C. van Voorst Vader, “Treatment of syphilis: the European view”, key question 3: “Is BBP 2.4 MU im on day 1, 8 and 15 sufficiently effective in late latent syphilis and is there an indicator for CSF examination in late latent HIV-infected syphilis patients before treatment?”):

1) CSF examination to exclude asymptomatic neurosyphilis (having clinically excluded symptomatic neurosyphilis, including auricular and ocular syphilis), possibly using criteria as non-treponemal serum RPR (or VDRL) test titre ≥ 1:32 and CD4+ cell count < 350/µL for patients at risk for asymptomatic neurosyphilis, followed by i.v. penicillin (or possibly ceftriaxone) treatment, if asymptomatic neurosyphilis is diagnosed in order to prevent the development of symptomatic neurosyphilis.[3] An additional criterion might be a quantitative TPHA, as our investigations in Vienna showed, that a serum TPHA titre <1:640 (which might be a TPPA titre of <1:640 or <1:1280) makes neurosyphilis highly unlikely, thus argues against CSF examination.

2) no CSF examination (also having excluded clinically asymptomatic neurosyphilis, including auricular and ocular syphilis), but 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. at least 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.

• Examination of CSF: TPPA (qualitatively), FTA-abs. test (qualitatively), VDRL test (quantitatively), total protein, albumin level, number of mononuclear cells. Quantitative TPPA and measurement of IgG and IgM level in CSF can also be performed, together with measurement of albumin, IgG and IgM level in serum. The formerly used TPHA has generally been replaced since circa 1999 by the TPPA.

• Extra parameters in CSF: IgG-index, IgM-index, albumin quotient. The use of the different TPHA/TPPA-indexes and ITpA-indices has been controversial. The value of the PCR for determination of the presence of T. pallidum antigen(s) in CSF and diagnosis of neurosyphilis is rather disappointing.

• The IgG-index decreases after adequate therapy, but may remain abnormal, as well as the TPPA-index and the albumin quotient. IgM-index and the number of mononuclear cells in the cerebrospinal fluid should become negative or normal within 1-2 years. The CSF-VDRL test may or may not become negative following therapy.

• IgG-index (parameter for intrathecal IgG synthesis; normal value: <0.75):
  \[
  \text{IgG level (mg/l) in CSF} : \text{albumin level (mg/l) in CSF}
  \]
  \[
  \text{IgG level (mg/l) in serum} : \text{albumin level (mg/l) in serum}
  \]
• IgM-index (parameter for intrathecal IgM synthesis; normal value: <0.07):
  IgM level (mg/l) in CSF : albumin level (mg/l) in CSF
  IgM level (mg/l) in serum : albumin level (mg/l) in serum

• Albumin-quotient/ratio (parameter for disturbance of blood-brain barrier; normal value: <7.5):
  albumin level (mg/l) in CSF x 1000
  albumin level (mg/l) in serum

• TPHA-index Vienna 2000 (parameter for intrathecal synthesis of anti-\(T. pallidum\)-specific IgG):[4]*
  CSF TPPA titer
  Albumin quotient (value as above: albumin CSF/serum x 1000)

* This TPHA-index Vienna 2000 was shown to have a specificity of 100% and a sensitivity of 98.3% in one study centre involving 60 HIV-seronegative symptomatic neurosyphilis patients and controls.[4] This index demonstrates the presence of intrathecal production of \(T. pallidum\) specific antibodies. This leaves the question of reproducibility of the CSF-TPHA in different laboratories (appears to be good). According to data acquired since 2001 by the same center in Vienna from 461 patients, the sensitivity of the test again was >98%, in symptomatic as well as asymptomatic neurosyphilis, and in the Vienna experience the cut-off value did not change when the TPHA was replaced by the TPPA in late latent syphilis patients. Confirmation of the value of the TPHA/TPPA-index Vienna 2000 by another group would be commendable. The influence of HIV-infection on this index is unknown.

• Criteria for the diagnosis of (symptomatic or asymptomatic) neurosyphilis:[2,4, and additional data from the Vienna center since 2001]

  TPHA/TPPA and/or FTA-abs test positive (in CSF)
  and
  increased number of mononuclear cells (> 10/mm\(^3\) in CSF)
  plus
  IgG-index ≥ 0.70 (in CSF)
  or
  positive VDRL test (in CSF)
  or
  TPHA-index Vienna 2000 >70*

* TPHA-index (Vienna 2000) >70: neurosyphilis highly probable.[4, and additional data from the Vienna center since 2001]

• Other considerations
  - A positive TPHA/TPPA or FTA-abs. test in CSF by itself does not confirm the diagnosis neurosyphilis, but a negative treponemal CSF test excludes neurosyphilis. As the CSF FTA-abs. test may be false positive, the TPHA/TPPA should be preferred.[5,6]
  - Finding in CSF a positive TPHA/TPPA, an increased number of mononuclear cells and a raised IgG- and/or IgM-index only provides circumstantial evidence for the diagnosis neurosyphilis. A positive CSF-VDRL test as well as a TPHA-index Vienna 2000 >70 are seen as providing more direct evidence for the diagnosis neurosyphilis, the sensitivity of the CSF-VDRL test being circa 85% (or lower) and of the TPHA-index Vienna 2004 >98% (data reported in this article).
  - The CSF VDRL test can be negative in neurosyphilis.
  - A CSF-TPHA titer >1:320 is indicative of neurosyphilis (found in 59/60, i.e. 98.3%, neurosyphilis patients), thus a CSF-TPHA titer <1:640 makes neurosyphilis unlikely.[4]
  - The IgG-index, indicating intrathecal IgG class antibody production if elevated, has high sensitivity for neurosyphilis, but low specificity (data reported in this article: IgG-index elevated in 113/114, i.e. >99%, neurosyphilis patients, but the IgG-index is generally elevated in any infectious disease with Central Nervous System (CNS) involvement).
  - The number of mononuclear cells in CSF can be normal in neurosyphilis, especially in parenchymatous neurosyphilis (late syphilis: tabes dorsalis, general paresis).
  - Tests may be performed for the presence of HIV-RNA or HIV-p24 Ag in CSF of HIV-infected individuals, which indicate HIV-infection of the central nervous system.
  - The criteria outlined above (except the CSF-VDRL test) have not been validated in HIV-seropositive patients.
- CSF abnormalities suggestive of asymptomatic neurosyphilis occur in about 20-30% of patients with early syphilis,[7,8] but the clinical relevance of that finding is very limited, as standard treatment for early syphilis is very effective.

**Key question 1. How valid is a positive CSF-VDRL for diagnosing neurosyphilis?**

A positive CSF-VDRL test is included in the CDC recommendations for neurosyphilis besides a CSF-protein value of > 0.45 g/L and pleiocytosis (> 5 cells/mm³).[1] The specificity is nearly 100%. Sensitivity however was between 30 and 80%.[9-11] In one of the larger studies, including 241 patients with neurosyphilis, the CSF-VDRL test was reactive in 43 % of patients.[10] Most of the studies published during recent years in the US defined neurosyphilis by a reactive CSF-VDRL test and were unable to check the sensitivity of the test.[13,14] We found 15 non-reactive CSF-VDRL test patients (6/15 asymptomatic) with neurosyphilis. Thus the sensitivity of a positive CSF-VDRL test for the diagnosis of neurosyphilis was 87%; the diagnosis neurosyphilis was missed by that criterion in 6/27 (22%) asymptomatic patients and in 9/87 (10%) symptomatic patients.

*Answer: A negative CSF-VDRL test does not exclude neurosyphilis. Additional tests for determining intrathecal production of specific (treponemal) antibodies are recommended.*

**Key question 2. How valid is a treponemal CSF test (TPHA/TPPA or FTA-abs. test) for diagnosing neurosyphilis?**

A negative treponemal CSF test (TPHA/TPPA or FTA-abs. test) excludes neurosyphilis.[3,5] As the CSF FTA-abs. test may be false positive, the TPHA/TPPA should be preferred.[5,6] A CSF-TPHA titer >1:320 is indicative of neurosyphilis (found in 59/60, i.e. 98.3%, neurosyphilis patients).[4] In 204 late latent syphilis patients a CSF-TPHA titre >1:80 was found in 9%, a CSF-TPHA titre >1:160 in 1.5%.

*Answer: A negative treponemal CSF test (TPHA/TPPA or FTA-abs. test) excludes neurosyphilis. The CSF-TPHA/TPPA should be preferred above the CSF-FTA-abs. test. A CSF-TPHA titre >1:320 is highly suggestive of the diagnosis neurosyphilis.*

**Key question 3. How valid is the TPHA-index Vienna 2000 for diagnosing neurosyphilis?**

The production of intrathecally synthesized antibodies can be measured by various indices, by which the amount of treponemal antibodies in CSF and in serum is related to either whole IgG (intrafetal T. pallidum antibody (ITPA) index, i.e. a treponemal antibody index with relative specific activity) or to the albumin quotient (TPHA-index, modified TPHA-index (mHA), MHA-TP index, i.e. treponemal antigen indices). Differences between these indices are mainly due to methodological aspects.[4] The sensitivity of all these indices is higher than that of the CSF-VDRL test. What is more important: in all 15 CSF-VDRL test negative patients intrathecally produced treponemal antibodies could be demonstrated by all indices applied. Using the TPHA-index Vienna 2000 (>70: neurosyphilis highly probable), the index with the highest sensitivity, the diagnosis neurosyphilis was missed in 1/114 patients (sensitivity 100% in asymptomatic neurosyphilis, 98.6% in symptomatic neurosyphilis). Specificity of the TPHA-index Vienna is very high, it being a specific treponemal test. Whether neuroborreliosis interferes with specificity is unknown. The cut-off value of the TPHA-index Vienna 2000 (>70) did not appear to be influenced by using the TPPA instead of the TPHA in late latent syphilis patients, according to the experience in the Vienna center. Confirmation of the value of the TPHA/TPPA-index Vienna 2000 by another group would be commendable. There are scarce data on the use of this test in HIV-infected patients.

*Answer: Measurement of intrathecally produced treponemal antibodies is more sensitive than the CSF-VDRL test and a specific index (preferentially the TPHA-index Vienna 2000) can be helpful for the laboratory diagnosis of neurosyphilis. The cut-off value (>70) did not appear to be influenced by using the TPPA instead of the TPHA. Confirmation of the value of the TPHA/TPPA-index Vienna 2000 by another group would be commendable.*

**Key question 4. How valid is CSF pleiocytosis for diagnosing neurosyphilis?**

Determination of the CSF leukocyte (WBC) count, i.e. the number of mononuclear cells, parameter for active cellular inflammation, is the most important for defining meningeal involvement. It is generally high in meningovascular neurosyphilis, but can be low in parenchymatous or asymptomatic neurosyphilis. We found >4 cells/mm³ in 110/114 (96 %) neurosyphilis patients, but also an elevated CSF leukocyte count in 13% of 204 late latent patients and in 8% of 81 early latent patients. The sensitivity of CSF pleiocytosis for diagnosing neurosyphilis was found by Hoosmand et al. to be 82%.[12] A higher cut-off value (not 5, but 10 cells/mm³) increases specificity but decreases sensitivity. The CSF leukocyte count is the main parameter for measuring the treatment response using CSF examination.
Key question 5. How valid is CSF protein for diagnosing neurosyphilis?
Elevated CSF protein (> 0.45 g/L) is one of the non-specific parameters indicating inflammation of the brain. We found elevated CSF protein in 113/114 patients with neurosyphilis, but also in 14% of 204 patients with late latent disease. In the study by Hoosmand et al. only 39% had elevated values. After treatment decline of CSF protein is slow.

Answer: CSF protein (parameter for inflammation) belongs to the standard CSF tests in neurology and is generally done with every sample. However, CSF protein is of little help in diagnosing neurosyphilis.

Key question 6. How valid is the albumin quotient for diagnosing neurosyphilis?
The ratio/quotient of CSF/serum albumin is a measure of the blood-brain barrier (BBB) function. Normal values are age dependent and generally <7.5. Dysfunction of the BBB is indicated by elevated values, indicating higher diffusion of albumin from the serum into CSF. Moskophidis and Müller found an elevated albumin-quotient in 93/215 (43%) neurosyphilis patients. We found an elevated albumin quotient in 60/114 (53%) patients with neurosyphilis and in 22% of patients with late latent syphilis.

Answer: The albumin quotient is of no help in diagnosing neurosyphilis, but is needed to determine the IgG-index and TPHA-index.

Key question 7. How valid is the IgG-index for diagnosing neurosyphilis?
This non-specific index calculates the relation of the CSF/serum IgG ratio to the albumin quotient/ratio. Elevated values indicate intrathecal IgG synthesis. Values of <0.75 are considered normal. The IgG-index is generally elevated in any infectious disease with CNS involvement. We found high sensitivity (96%) in the neurosyphilis group (1/114 patients with neurosyphilis did not have an elevated IgG-index), but an elevated value (>0.75) was also found in 73% of 204 patients with late latent syphilis (these patients all had brain diseases not associated with syphilis). Van Eijk et al. found an elevated IgG-index in 13/21 (62%) patients with symptomatic neurosyphilis and in 4/159 (3%) patients with late syphilis.

Answer: This non-specific index is highly sensitive for intrathecal antibody production, but specificity for diagnosing neurosyphilis is low. It should be supplemented by an index measuring specific intrathecal antitreponemal antibody production.

Key question 8. Is it worthwhile to use the IgM-index for diagnosing neurosyphilis?
The IgM-index is calculated in a way similar to the IgG-index, but IgG is replaced by IgM. A positive index has a high positive predictive value, but IgM concentrations in CSF are very low and quantification is not easy. In our study specific IgM production was found in only one third of patients with active disease (neurosyphilis), which agrees with the findings of others.

Answer: The IgM-index lacks sensitivity and is not very valuable for the diagnosing neurosyphilis.

Key question 9. How valid is a PCR for Treponema pallidum DNA in CSF for diagnosing neurosyphilis?
Demonstration of Treponema pallidum specific DNA in CSF is a strong indicator of active disease. However, one can detect specific DNA by highly sensitive nested PCR in only about one half of patients with neurosyphilis. In addition, Treponema pallidum DNA could be detected in some patients for up to 3 years after adequate treatment.

Answer: A PCR for Treponema pallidum DNA is of little help for standard diagnosis of neurosyphilis.

Key question 10. How should one monitor the treatment response in CSF after treatment for neurosyphilis?
Decline of treponemal antibody titres (TPHA/TPPA, FTA-abs. test) in CSF and serum can be seen in most patients, but only a minority becomes negative. The same is true for all specific indices. A two-fold decline of CSF-VDRL within 3 months is a good indicator for efficacy of treatment, however, long lasting reactivity, especially in patients with late (parenchymatous) neurosyphilis (tabes dorsalis, general paresis) is not unusual. In HIV-infected patients the CSF-VDRL test has been reported to be 2.5 times less likely to normalize after treatment compared to HIV-negative patients, while CSF-VDRL reactivity was also less likely to normalize with higher baseline values. Return to normal values of CSF-protein and non-specific indices is slow. The best parameter is the follow-up of pleiocytosis: the decline in CSF leukocyte (WBC) count (i.e. of mononuclear cells)
is rapid and values <5 cells/mm<sup>3</sup> are generally reached within 3 months in most patients, but baseline CSF pleocytosis in HIV-infected patients may interfere with a reliable interpretation of this test (see paper nr 4: M. Janier, “Syphilis and HIV-infection: the European view”).

**Answer:** Measurement of the CSF leukocyte count (i.e. of mononuclear cells) is the most useful parameter for assessing treatment response in neurosyphilis.

**Key question 11. Which tests should be recommended for use for laboratory diagnosis of neurosyphilis?**

CSF leukocyte count and CSF protein are routine tests in every neurological department. Despite low specificity, they do indicate inflammation within the CNS and should be included in the diagnosis of neurosyphilis. The CSF leukocyte (mononuclear cell) count is essential, as it is also used for monitoring treatment response. Measurement of CSF IgG should be preferred above CSF protein measurement, as an elevated CSF IgG-index indicates intrathecal IgG synthesis, which is found in the large majority of neurosyphilis patients, which is not the case for elevated CSF protein. An elevated IgG-index can occur in any inflammatory CNS process, however, limiting specificity. In order to measure the IgG-index (and the TPHA-index Vienna 2000), one needs the albumin quotient, which measures the blood-brain-barrier function. *Treponema pallidum* specific antibody tests are highly sensitive, but a positive treponemal CSF test (preferably TPHA/TPPA) does not indicate active disease. A CSF TPHA titer >1:320, however, indicates neurosyphilis. Most important, a negative treponemal CSF test does exclude neurosyphilis. The CSF-VDRL test lacks sensitivity, but specificity is high. All treponemal indices have a higher sensitivity than the CSF-VDRL test. Such a test, preferably the TPHA-index Vienna 2000, being the most sensitive test in the Vienna experience, can be helpful in the laboratory diagnosis of neurosyphilis.

**Answer:** a) CSF leukocyte (i.e. mononuclear cell) count (parameter for inflammation, main parameter for monitoring treatment response); b) albumin quotient (parameter for blood-brain-barrier function and necessary for measuring IgG-index and treponemal antibody index); c) IgG-index (measure for intrathecal non-specific antibody production, more sensitive than CSF protein); d) CSF-TPHA (if negative, neurosyphilis is excluded; if titer >1:320, neurosyphilis is highly likely); e) TPHA-index Vienna 2000 (may be helpful; measure for intrathecal specific antitreponemal antibody production; if >70: neurosyphilis highly probable). For albumin quotient and IgG-index a serum sample is needed besides a CSF sample.

**Key question 12. What is the importance of diagnosing asymptomatic neurosyphilis in patients with late latent syphilis or latent syphilis of unknown duration and in patients with early syphilis with symptomatic ocular or auricular syphilis?**

The American syphilis guideline 2002 recommends prompt CSF examination in patients with latent syphilis, who demonstrate any of the following criteria:[1] a) neurologic or ocular signs or symptoms; b) evidence of tertiary syphilis (e.g. aortitis, gumma, iritis); c) treatment failure; d) HIV-infection with late latent syphilis or syphilis of unknown duration.

The European syphilis guideline 2001 recommends CSF examination for patients with:[2] a) clinical evidence of neurological involvement; b) ocular, cardiovascular or gummatous syphilis; c) concomitant HIV infection.

The European syphilis guideline 2001 and the American CDC syphilis guideline 2002 and also Rompalo’s 2004 “Update on syphilis and HIV” thus recommend CSF examination before treatment in HIV-infected patients with late latent syphilis or latent syphilis of unknown duration.[1,2,22] Hard data on the magnitude of the risk of developing symptomatic neurosyphilis from asymptomatic neurosyphilis after standard treatment with BBP 2.4 MU i.m. on day 1, 8 and 15 in these patients were not given though. The risk of asymptomatic neurosyphilis as diagnosed by a positive CSF VDRL test appears to be increased in patients dually infected with HIV and syphilis, but does that result in a risk of symptomatic neurosyphilis of such magnitude that standard CSF examination should be recommended of HIV-infected patients with late latent syphilis or latent syphilis of unknown duration? That strategy may not be cost-effective and leads to finding CSF abnormalities (concurrent HIV-infection!), which are difficult to interpret.[23,24] Criteria as non-treponemal serum RPR (or VDRL) test titre ≥ 1:32 and CD4+ cell count < 350/µL may increase the risk for asymptomatic neurosyphilis and help selecting patients for elective CSF examination.[3] An additional criterion might be a quantitative TPHA, as investigations in the Vienna center showed, that a serum TPPA titer <1:640 (which might be a TPPA titer of <1:640 or <1:1280) makes neurosyphilis highly unlikely, thus argues against CSF examination. If CSF examination is not performed (it is often refused by the patient), an alternative option is clinical and serologic follow-up of these patients, which is generally performed at HIV-clinics because of the HIV-infection, and instruction when to contact the physician.

As patients with early syphilis with symptomatic ocular or auricular syphilis (without other symptoms of CNS involvement) are generally treated with i.v. penicillin, it is not essential to perform CSF examination in these patients, which may demonstrate CSF abnormalities consistent with neurosyphilis (more frequent in ocular than in auricular syphilis), as concomitant CSF abnormalities, if present, are treated concurrently.
For further information, see: a) paper nr 2: R. Parkes and P.C. van Voorst Vader, “Treatment of syphilis: the European view”, key question 3: “Is 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 syphilis of unknown duration before treatment?”; b) paper nr 3: P. French, “Serologic follow-up after treatment for syphilis in Europe”, key question 5: “How should HIV-negative and HIV-positive individuals with an inadequate serologic response after treatment of late latent syphilis be managed?”; c) paper nr 4: M. Janier, “Syphilis and HIV-infection: the European view”, key question 4: “Should CSF examination be performed in HIV-positive patients with late latent syphilis or latent syphilis of unknown duration?”.

Answer: European 2001 and American 2002 syphilis guidelines recommend CSF examination before treatment in HIV-infected patients with late latent syphilis or latent syphilis of unknown duration to exclude asymptomatic neurosyphilis, but there are no hard data on the magnitude of the risk of developing symptomatic neurosyphilis after standard BBP treatment on day 1, 8 and 15 of these patients. If CSF examination is not performed, an alternative option is clinical and serologic follow-up of these patients during 1-2 years after treatment or longer, which is generally performed at HIV-clinics because of the HIV-infection, and instruction when to contact the physician. CSF examination is indicated in patients with symptoms possibly caused by neurosyphilis, but is not essential in patients with symptomatic ocular or auricular syphilis (without other symptoms of CNS involvement), if they are treated with i.v. penicillin.

References 5-22
22. Rompalo A. Treatment and prevention of syphilis in the HIV-infected patient. 2004; www.uptodate.com