Independent Appraisal and Review of ILADS 2004 'Evidence-based guidelines for the management of Lyme disease'

8 December 2010

Executive Summary

At the request of the Chief Executive of the Health Protection Agency (HPA) an independent working group chaired by Professor Brian Duerden CBE, Inspector of Microbiology and Infection Control, Department of Health, reviewed the International Lyme and Associated Diseases Society's (ILADS) *"Evidence-based guidelines for the management of Lyme disease*" (Cameron *et a*l. Exp Rev Anti-infect Ther 2004;2:S1-13). The review group was convened in order to assess whether the guidelines were suitable for use in the UK and should be referenced by the HPA, in response to concerns raised by clinicians and patients. The panel consisted of experts in the fields of general practice, infectious diseases, microbiology, parasitology, neurology and rheumatology, all with considerable experience in the diagnosis and management of Lyme borreliosis. The review process included a detailed assessment of the guidelines' content and of the references cited in support of the guidelines.

Areas in the ILADS guidelines highlighted for special consideration by the panel included:

- Case definition
- Clinical diagnostic criteria
- Laboratory diagnostic criteria
- Treatment recommendations
- Potential for benefit or harm to patients from use of the guidelines

The panel concluded that:

- The ILADS guidelines are poorly constructed and do not provide a scientifically sound evidence-based approach to the diagnosis and care of patients with Lyme borreliosis.

- The ILADS working group does not provide evidence that it used a Cochrane-based or similar approach in developing the guidelines. Some references do not provide evidence to support statements for which they were cited in the guidelines. Some good-quality peer-reviewed articles are selectively quoted, using sub-group analyses without regard for the broader findings of the full studies. Some references were published in an advocacy group-sponsored journal that was not Medline-listed, others are available only as conference / symposium abstracts or are unpublished. Some reference citations are inaccurate, demonstrating poor attention to detail.

Case definitions

The ILADS guidelines' case definitions for Lyme disease are confused, lack specificity and are potentially dangerous, because their use can result in a high risk of misdiagnosis. The Lyme disease symptom list is non-specific and unhelpful, particularly for what the ILADS authors refer to as chronic Lyme disease.

Clinical diagnostic criteria

The ILADS guidelines authors acknowledge the poor specificity of the clinical diagnostic criteria through their admission that case presentations attributed to Lyme disease using their criteria can be identical to other multisystem disorders, including systemic lupus erythematosus, rheumatoid arthritis and fibromyalgia. They also include neurologic features such as demyelinating disease, neuropsychiatric presentations and sometimes motor neurone disease, but do not offer any evidence to substantiate a causative role for *Borrelia burgdorferi* infection in these conditions. Furthermore, the symptom list is so broad-ranging and nonspecific that its application could result in many patients being diagnosed as potential cases of "chronic Lyme disease" without any definitive evidence of *B. burgdorferi* infection.

Laboratory diagnostic criteria

The ILADS guidelines contain misleading information regarding laboratory diagnostic criteria for the diagnosis of Lyme borreliosis. It is well-recognised that laboratory tests have only a limited place in supporting a diagnosis of erythema migrans, but modern-generation antibody tests have a high degree of sensitivity in later stages of infection. Internationally-accepted tests and interpretative criteria were developed for diagnostic purposes. They were not developed primarily for epidemiological or research purposes, as stated incorrectly in the ILADS guidelines. The ILADS guidelines do not offer adequate evidence to support the use of less specific immunoblot criteria than those recommended by international authorities.

Treatment recommendations

The ILADS guidelines authors do not provide credible evidence to support their treatment recommendations, which include prolonged use of oral or parenteral antibiotics, singly, sequentially or in combination.

There is potential for harm from use of ILADS guidelines.

- Patients with other serious conditions who receive a misdiagnosis of Lyme disease through use of ILADS guidelines risk losing opportunities for diagnosis and treatment of their illnesses.

- Patients receiving prolonged antibiotic treatments are at risk of organ damage from adverse effects of the drugs as well as risk of secondary infections such as *Clostridium difficile* entercolitis, multi-resistant Gram-positive or Gram-negative bacterial infections and fungal infections. Patients receiving prolonged treatment with parenteral antibiotics have additional infection-related and other risks associated with long-term intravascular access devices.

- Other potential harms to patients associated with misdiagnosis include psychological damage through fixation on an unsubstantiated diagnosis of Lyme disease and financial hardship from recommendation and provision of repeated and prolonged courses of oral or parenteral antibiotics that doctors providing NHS treatment do not consider appropriate for provision under the NHS. This can also lead to breakdown of relationships between patients and their NHS doctors.

The panel recommends that:

- the HPA should not include the ILADS guidelines in the list of guidelines and other references recommended by the HPA for help and support in the diagnosis and management of Lyme borreliosis.

- the HPA should consider providing a warning against the use of the ILADS guidelines as part of its health protection function, in view of the potential risk to patients from misdiagnosis and inappropriate treatment.

Summary of the Review Panel's findings

The review group conducted a critical review of the ILADS guidelines (Cameron *et al*, 2004) from the perspectives of the reliability of the evidence base in respect of the clinical manifestations, pathology and natural history of Lyme disease; the appropriate and validated use of clinical and laboratory diagnostic criteria; and the effectiveness and safety of the recommended treatment.

Background: the natural history of Lyme borreliosis, its diagnosis and management

Lyme borreliosis is the direct consequence of infection with the spirochaete *Borrelia burgdorferi* sensu lato, acquired as a result of a person being bitten by a tick carrying *B burgdorferi*. The acute infection generally comprises erythema migrans, an erythematous rash spreading from the site of a tick bite. In its typical form this rash is readily diagnosed by clinical observation and examination. Laboratory diagnostic tests are not required routinely for the diagnosis of erythema migrans, but they can be helpful in occasional atypical cases. It is readily acknowledged that serological tests may be negative at this early stage of infection, as an antibody response can take several weeks to develop. In some untreated patients *B burgdorferi* can spread to other organs and tissues and cause presentations of disseminated disease, principally affecting the nervous and musculoskeletal systems and the skin. Laboratory support is required for diagnosis of disseminated and late manifestations of Lyme borreliosis as no clinical feature of later-stage disease is unique to *B burgdorferi* infection. Case definitions giving detailed descriptions of clinical features and laboratory diagnostic criteria for Lyme borreliosis in Europe were published in 1997 and have recently been revalidated. (Stanek G *et al*. 2010) Long-term objective and subjective sequelae were also reviewed in that publication.

Specialist societies and national authorities in Europe and North America have published evidence-based treatment guidelines and consensus documents, and a comparison of first-line treatments is summarised in O'Connell 2010. The most recent guidelines are from the European Federation of Neurological Societies (Mygland *et al* 2010). The great majority of *B. burgdorferi* infections, including most presentations of acute neuroborreliosis (the most common complication seen in the UK) can be treated successfully with relatively short courses of oral antibiotics (ten to 28 days, depending on clinical presentation). Parenteral treatment for two to three weeks is recommended for encephalitis or myelitis and for rare cases of arthritis.

It is well-recognised that some patients may have residual symptoms and objective clinical findings following treatment. Patients who sustained severe tissue damage prior to treatment may improve only slowly and incompletely. (Kruger *et al*. 1989; Ljostad and Mygland 2010) Occasional patients with facial palsy have some residual paresis. (Skogman *et al*. 2008) Some patients can have persistent non-specific symptoms such as fatigue, headaches, myalgias, arthralgias for some time without clinical or laboratory evidence of continuing active infection. (Marques 2008) Similar symptoms can occur following other systemic infections. (Hickie *et al*. 2006) The incidence of prolonged post-infection symptoms associated with Lyme borreliosis is

unclear, but recent prospective European studies incorporating uninfected control groups showed good outcomes for the great majority of patients with appropriately treated Lyme borreliosis. The incidence of long-term subjective symptoms appeared to be similar in patients and uninfected controls. (Skogman *et al*. 2008; Cerar *et al*. 2010)

General comments on the ILADS guidelines and their development

The ILADS guidelines did not undergo independent peer review prior to publication. They were published as a supplement to a peer-reviewed journal, but did not undergo the journal's standard peer-review process. (Manzotti 2006; personal communication on file)

They are poorly constructed and do not have a sound evidence base

Development of evidence based medicine guidelines is a process that usually consists of the following steps:

1. explicitly defining a question
2. explicit statement of a method of assessing quality of evidence
3. systematic review of all available evidence and determination of the data that meets minimum requirements for inclusion
4. review of selected data, assigning each study a class of evidence, using predefined criteria (see methodologic examples in the Appendix)
5. aggregating the data to reach conclusions, grading each conclusion based on the strength of the available evidence. The Appendix gives examples of evidence grading for guidelines from the Infectious Diseases Society of America (IDSA), the American Academy of Neurology (AAN) and ILADS.

Criteria for inclusion and exclusion of data in the ILADS guidelines

The ILADS Guidelines data acquisition process was described as follows: *"Our data sources are English-language articles published from 1975 to 2003. The selection panel synthesized the recommendations from published and expert opinion. Human studies of Lyme disease were identified from MEDLINE (1975 to 2003) and from references in pertinent articles and reviews. Also included are abstracts and material presented at professional meetings and the collective experience of the ILADS Working Group treating tens of thousands of Lyme disease patients."*

The ILADS guidelines authors do not list explicit criteria for inclusion or exclusion of data. They do not indicate how many studies were reviewed, and do not specify how many were accepted and rejected and the reasons for these decisions. Guidelines generally restrict data sources to peer reviewed publications, because abstracts and meeting presentations rarely contain sufficient information to assess study validity. Some references used in support of the ILADS guidelines were published in an advocacy group-sponsored journal that was not Medline-listed and is no longer published (Journal of Spirochetal and Tickborne Diseases). Others are poor-quality conference abstracts or appear in symposium supplements without having undergone a full peer-review process and others are unpublished. Examples include ILADS guidelines references 16, 17, 19, 21, 34, 47, 57, 58, 62.

There is evidence of selective quotation from good-quality peer-reviewed articles; in particular sub-group analyses are used without regard for the broader findings of the full studies. Examples include ILADS references 24, 27.

Many of the studies cited by the ILADS authors to support their view that the outcome of Lyme disease treated by current standard recommendations is poor were performed in patients infected in the 1970s and 1980s. Many of those early study participants were untreated or had inadequate treatment by modern standards. Examples include ILADS references 3, 4, 12, 24. The ILADS guidelines authors ignored the findings of studies showing that the major reason for non-response to treatment for Lyme disease is misdiagnosis (ILADS references 63, 64). Other references do not support ILADS guidelines statements and are inappropriately cited. Examples include ILADS references 10, 37, 38, 39, 40, 44, 45, 46. Some references are inaccurately cited.

Evidence ratings and tables in the ILADS guidelines

The ILADS authors stated that they used a method of evidence rating. They did not include an evidence table or any indication of how they rated any of the information they included in their reference list. In the absence of any such information, a Review Panel member assessed the quality of evidence in the ILADS-referenced studies, using the American Academy of Neurology (AAN) classification system.

AAN classification (see the Appendix for a more detailed description)
Class I: Randomised, controlled clinical trial with masked or objective outcome assessment in a representative population
Class II: Prospective matched group cohort study in a representative population with masked outcome assessment or a randomised controlled trial in a representative population
Class III: All other controlled trails in a representative population where outcome is independently assessed or independently derived by objective outcome measurement.
Class IV: Contains too little information to assess methodologic validity.

The ILADS guidelines reference list indicates inclusion of 66 studies which can be divided into eight types (table 1).

Table 1. Categorisation of the studies included in the ILADS guidelines

Type of study	Description	Number of studies
1	Studies included and rated in the 2000 IDSA guideline (Wormser *et al.* 2000).	11
2	Studies in progress, with no accrued data to date.	2
3	ILADS website.	1
4	Abstracts, meeting proceedings or other non-Medline listed material. These can be categorized as AAN Class IV, as containing too little information to assess methodologic validity.	9
5	Review articles and other material expressing opinions but not data. These can also be categorised as AAN Class IV.	16
6	Studies not related to treatment of Lyme disease.	18
7	Studies demonstrating that excessive treatment is bad.	4
8	Papers addressing treatment and not included in the 2000 IDSA Guidelines (Wormser *et al*. 2000).	5 (see details in table 2)
Total		66

The reasons why five treatment studies included in the ILADS guidelines were omitted from the IDSA 2000 guidelines are given in table 2.

Table 2. Studies included in ILADS guidelines that were omitted from the 2000 IDSA guidelines

ILADS reference number	Authors	Reason for omission from 2000 IDSA guidelines.
18	Cimmino and Accardo 1992	An anecdotal description of two patients with Lyme arthritis (AAN Class IV).
20	Lawrence *et al*. 1995	A case report of one patient (AAN Class IV).
29	Petrovic *et al.* 1998	An observational study of four patients (AAN Class IV.)
41	Barsic *et al*. 2000	A comparative study showing equivalence of doxycycline and azithromycin treatment (i.e. not relevant).
61	Wahlberg *et al*. 1994	A non-randomized, non-blinded treatment of 100 patients with “late Lyme disease”; with limited definitions of “late Lyme disease” or “treatment response”. (At best this is AAN Class III evidence).

In summary, the literature cited in the ILADS guidelines but omitted in the IDSA 2000 guidelines adds no AAN Class I or Class II evidence to those cited by the 2000 IDSA

guidelines. The literature adds only one Class III and a number of Class IV studies. Class III or IV evidence generally cannot lead to high level recommendations.

Despite the absence of any additional high level data, the ILADS guideline consistently gives higher grades to recommendations compared to those of the IDSA (Cameron *et al* 2004; Table 1). This is at variance with all standard evidence based medicine methodology.

ILADS Clinical case definitions

The ILADS case definitions are poorly constructed, incoherent and unsupported by credible peer-reviewed evidence.

The list of Lyme disease symptoms given in the guidelines comprises many non-specific symptoms. The ILADS guidelines authors state that the clinical presentation of what they consider to be "chronic Lyme disease" can be identical to those of other multisystem disorders, including systemic lupus erythematosus, rheumatoid arthritis, fibromyalgia and chronic fatigue syndrome. They also include neurologic disorders such as demyelinating disease, sometimes motor neurone disease as well as neuropsychiatric presentations as being consistent with chronic Lyme disease, but do not offer any evidence to substantiate these claims. The authors do not address the likelihood that their poorly specific criteria will result in over-diagnosis of Lyme disease and missed opportunities for accurate diagnosis and treatment for patients who have other conditions.

Diagnostic tests

The ILADS guidelines authors ignore the large body of published peer-reviewed evidence showing that laboratory tests are valuable and reliable in support of a diagnosis of disseminated Lyme disease. Antibody tests performed to internationally agreed and validated criteria have a high sensitivity in established infection. and patients with late-stage Lyme borreliosis are rarely seronegative. (Stanek *et al*. 2010; Wilske *et al*. 2007; Aguero-Rosenfeld *et al*. 2005; MiQ 2000). The evidence-based serological diagnostic approach requires a two-tier test system. A sensitive but insufficiently specific initial screening test for *B. burgdorferi* antibodies is followed by supplementary testing of samples giving reactive or equivocal results in the initial test, to assess the specificity of reactions. Immunoblots are widely used as second-stage tests and strict interpretative criteria are important to ensure appropriate specificity tests and avoid false positive interpretations.

The ILADS guidelines recommendation for using tests with lower specificity increases the risk of misdiagnosis and potential harm. Examples include immunoblots interpreted using unvalidated and less stringent criteria on specimens that had not undergone first-stage (screening) testing, or which had tested negative in first-stage tests. Other unreliable tests include lymphocyte transformation tests, CD-57 tests, urinary antigen detection, spirochaete detection by microscopy and PCR applied to blood and urine. (Marques *et al* 2009; Wilske *et al*. 2007; Duerden

2006; Anon 2005; Aguero-Rosenfeld *et al*. 2005; Klempner *et al*. 2001a; Marques *et al*. 2000)

Microbiological evidence

The ILADS guidelines authors advocate prolonged antibiotic therapy for patients with "chronic Lyme disease" diagnosed by the non-specific ILADS criteria, on the basis that they believe that there is ongoing active infection, but they offer no supporting microbiological evidence to support this approach. Studies such as those of Klempner et al (Klempner *et al*. 2001b – *ILADS reference 23*) performed thorough and detailed investigations using validated and sensitive methods to seek evidence of active infection in patients with persistent symptoms following previously treated infections. No evidence was found to support the proposition that these patients had persistent active infection, and antibiotic treated patients had similar outcomes to those receiving placebo. More recent studies of prolonged treatments have shown no sustained benefit to patients with persistent symptoms. (Fallon *et al*. 2008 [*ILADS reference 57* – unpublished at the time of ILADS guidelines publication]; Oksi *et al*. 2007; Krupp *et al*. 2003) Other studies have shown that *Borrelia burgdorferi* has not shown development of resistance to antibiotics recommended in standard guidelines. Experience with syphilis (another spirochaetal infection with early and late disease manifestations) has shown good success rates using appropriate antibiotic regimens for limited periods. (Tramont, 2010) ILADS fails to present evidence for active infection in "chronic Lyme disease" in support of the recommendation for use of potentially hazardous prolonged treatment for patients.

Antibiotic treatment

The ILADS guidelines authors give no coherent guidance on the type and duration of antibiotic treatment. There is no logical reason to use benzathine penicillin, which does not reliably achieve good CSF levels (Tramont 2010), in patients with "chronic Lyme disease" a disorder suggested by some to be due to nervous system infection. Oral doxcycline or parenteral ceftriaxone have been shown to be effective for neuroborreliosis. (Mygland *et al*. 2010) The ILADS guidelines authors offer no credible peer-reviewed scientific support for using agents such as metronidazole or imipenem, or for the use of combinations of two or more antibiotics in the treatment of Lyme borreliosis. No evidence is provided to support the prolonged use of antibiotics such as amoxicillin, doxycycline or azithromycin at much higher doses than usual.

The guidelines recommend continuation of antibiotic treatment until all symptoms have resolved. Lack of response to standard treatment should be an indication to review the diagnosis rather than taken as an indication for prolonging antibiotic treatment, especially when ILADS' poorly specific diagnostic criteria have been applied. (Wormser *et al*. 2009; Hassett *et al*. 2009; Carrington-Reid *et al*. 1998- *ILADS reference 63*; Steere *et al*. 1993- *ILADS reference 64*)

The ILADS authors also fail to acknowledge that numerous peer reviewed studies, including some quoted in their guidelines (eg ILADS guidelines references 12, 51,

52), showed that response to appropriate treatment in previously untreated or inadequately treated later-stage Lyme borreliosis can continue for some time after a treatment course has finished, and that response may be incomplete if there was severe tissue damage prior to treatment. Lack of immediate complete response should not be used as an indicator of treatment failure, and it is not an indication for long-term treatment

The authors did not sufficiently consider non-antimicrobial effects of antibiotics such as tetracyclines, macrolides and ceftriaxone, which include anti-inflammatory, anti-arthritic or neuroprotective effects. (Rothstein *et al*. 2005; Rubin and Tamaoki 2005) These agents can have some disease-modifying effects when used by patients with inflammatory or autoimmune disorders or even neurological conditions such as motor neurone disease who have been misdiagnosed as having Lyme disease by the poorly-specific ILADS criteria.

The authors did not consider placebo effects or the natural history of variation of symptomatology in patients with chronic fatigue syndrome, fibromyalgia or other longterm conditions (Klempner *et al*. 2001; Tilley *et al*. 1995)

Potential for harm through use of ILADS guidelines

Patients with other serious conditions misdiagnosed as “chronic Lyme disease” using the poorly specific ILADS guidelines risk losing opportunities for appropriate diagnosis and management. Patients misdiagnosed and mistreated for “chronic Lyme disease” include those with longstanding, painful and debilitating conditions such as multiple sclerosis, rheumatoid arthritis or other autoimmune diseases. Some have life-threatening conditions such as motor neurone disease. (ALSUntangled Group, 2009) A diagnosis of “chronic Lyme disease” holds out the hope of a potentially treatable condition to these vulnerable groups of patients and their families. If non-response to treatment is used as an indication for more treatment, many patients may endure months or years of inappropriate therapies for no benefit. This can cause physical and psychological harm, with some patients and their families also facing considerable financial hardship through self-funding of expensive treatments.

Furthermore, there are significant hazards associated with inappropriate antibiotic treatment, particularly from long-term use of broad spectrum agents. (Holzbauer *et al* 2010; Hassett *et al* 2009; Patel *et al*. 2000; Carrington-Reid *et al*, 1998; Ettestad *et al*. 1995). These include toxicity of the agents, hypersensitivity (allergy), and predisposition to infection with *Clostridium difficile* or antibiotic-resistant bacteria.

Children misdiagnosed with “chronic Lyme disease” are a particularly vulnerable group, and one of the references cited by the ILADS guidelines authors (ILADS guidelines reference 17) illustrated the dangers of misdiagnosis and gross and painful mistreatment. Experience from other clinicians has indicated that some children diagnosed as having “chronic Lyme disease” according to the ILADS criteria received oral and parenteral antibiotics for years, and had unnecessary interruption of schooling and social development, to the extent that there has been a loss of childhood. Serious physical harm to children from adverse events related to over-

use of broad spectrum antibiotics for unsubstantiated Lyme disease has also been well-documented. (Ettestad *et al*.1995)

Many people suffering from medically unexplained chronic conditions such as chronic fatigue syndrome and other illnesses are desperate for an explanation and possible cure for their illnesses. They provide a ready customer base for any treatment that holds out promise of a cure, however lacking in evidence. The widespread use of the unreliable ILADS clinical guidelines in this large group of patients would result in inappropriate treatment and potentially serious morbidity.

Conclusions of the Review Panel

The ILADS guidelines are not evidence-based and are poorly constructed.

Application of the ILADS guidelines' poorly defined case definitions will result in a very high risk of misdiagnosis.

Use of ILADS guidelines' vague treatment recommendations, including prolonged use of antibiotics, has potentially serious consequences.

Patients misdiagnosed with Lyme disease risk losing opportunities for diagnosis and treatment of other conditions. They also risk serious physical, psychological social and financial adverse events.

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Appendix: Examples of evidence grading:

IDSA Guideline
(Wormser G, Dattwyler R, Shapiro ED et al. The clinical assessment, treatment and prevention of Lyme disease, human granulocytic anaplasmosis and babesiosis: clinical practice guidelines by the Infectious diseases Society of America. CID, 2006;43:1089-1134)

Quality of evidence
I Evidence from ≥1 properly randomized, controlled trial
II Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case controlled analytic studies (preferably from ≥1 center); from multiple time series studies; or from dramatic results from uncontrolled experiments
III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert Committees

American Academy of Neurology
(French J, Gronseth G. Lost in a jungle of evidence; we need a compass. Neurology 2008;71:1634-38)

Table Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
The following are also required:
a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required:

- The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).
- The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are substantially equivalent to those of previous studies establishing efficacy of the standard treatment.
- The interpretation of the results of the study is based on an observed-cases analysis.

Class II. A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks

one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above.
Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to a Class III.

ILADS

A rating of I indicates that at least one randomized controlled trial supports the recommendation; II, evidence from at least one well-designed clinical trial without randomization supports the recommendation; and III, 'expert opinion'. (The ILADS Working Group, 2004)