Reviewer's report

Title:A systematic review of serological outcomes after syphilis treatment in HIV-infected and HIV-uninfected persons: rethinking the significance of the serofast state

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Reviewer:Philipp P. Bosshard

Reviewer's report:

A. Sena et al. have made a systematic review of serological outcomes after syphilis treatment. The review overall summarizes important studies concerning syphilis management especially concerning serological outcome and is worth to be published. The subheadings in the results section give a clear structure. The manuscript is well written and understandable although eventually a bit long. However, the basic concept of the serofast state should be reconsidered (see below). I believe that the manuscript also when not focusing of this issue or when clearly separating the two conditions (patients which did not yet respond at e.g. 12 months and true serofast; see below) still has much valuable information for publication.

Major revisions:

1. The overall concept of the study to term different serological conditions as serofast is critical and not supported by most literature and in my opinion also misleading. The authors use “serofast” for actually two different situations which can (and should) be distinguished (lines 147 ff); 1) <4-fold decline in nontreponemal titers at 6 or 12 months OR 2) persistent nontreponemal titers after initial adequate decline.

However, condition 1) should not be termed “serofast” but rather “serological failure” (what is used in most literature) or eventually “non-responder” or simply “patients who have not yet responded” as studies have clearly shown that the percentage of those who reach the 4-fold reduction is time dependent (what the authors also describe on line 230ff). Also, current guidelines, e.g. CDC, European, avoid the term “serofast” for the non-responders. The two citations (18-19 on line 100) which should support the definition for “serofast” are critical as one is a self-citation and the other is the CDC guideline which gives not a clear definition but rather implies low residual antibodies without seroreversion, i.e., the second condition (see below).

In light of this, condition 1 is not a steady state. Therefore, serological failure is not an absolute or definite situation but rather is serological failure at a certain time. This should be discussed.

The second condition, persistent nontreponemal titers, could be termed “serofast”. Similarly, Clement et al (JAMA 2014) recently have defined “serofast” as a situation (after initial adequate decline) in which nontreponemal titers fail to
completely revert to nonreactive. Typically these titers stay on a low level, e.g. 1:2, 1:4 or 1:8.

I would suggest that either the byline in the title “rethinking…” is deleted (or renamed as “rethinking the significance of serological failures” or similar). And also the text should be adapted accordingly all over in the manuscript.

The authors themselves give evidence that serological response is strongly time dependent; after 6 months 79.5% responded and after 12 months 87.8%. And after 24 months even more would have reached the 4-fold decline. Unfortunately the data on page 13 about disease stage do not include late syphilis cases, but it is likely that the non-responders primarily are late syphilis cases which need more time to respond what has been shown previously. I encourage the authors to try to stratify the data also according to late syphilis.

2. Although the authors clearly state the eligibility criteria and how the literature was searched and how many abstracts were reviewed, I am surprised how many studies have not been found suitable or have been missed. I found 13 more studies which at first sight seem to fulfill the criteria, e.g. number of non-responders/serological failure at 6 or 12 months after therapy. In many cases factors which might influence the outcome have been evaluated, e.g. HIV, syphilis stage, baseline titers.

I strongly encourage the authors to review these papers and either use them in the study or in the answer to the editor give short notice why they were excluded.

Overview other studies (alphabetical):

Study, Journal, Size, 6 a/o 12 months data
Farhi et al 2009, Medicine, 144, y
Fröhlich Knaute et al 2012, CID, 264, y
Goeman et al 1995, Genitourin Med, 193, y
Gonzalez et al 2009, CID, 347, y
Gourevitch et al 1993, Ann Int Med, 50
Hutchinson et al 1994, Ann Int Med, 309, y
Janier et al 1999, Dermatology, 118, N
Kingston and Higgins 2003, STI Journal, 78, y
Long et al 2006, Sex Transm Dis, 76, y
McMillan and Young 2008, Int J STD AIDS, 229, Y
Riedner et al 2005, NEJM, 308, y
Telzak et al 1991, AIDS, 624, y
Yinnon et al 1996, Arch Int Med, 128, y

Minor revisions:
1. Line 86: Nontreponemal tests are used for syphilis screening in the U.S. (in many European countries treponemal tests are used, also in the guideline). This
has to be stated properly

2. Line 143: Sentence unclear; only paper that included proportions of response were included?

3. Lines 284ff: You say “Five studies…”, but I count seven in the paragraph.

4. Line 312ff: Delete “While” or “however” in this sentence.

5. Lines 452ff: One important explanation (according to major point 1) is missing; patients may eventually have not responded after 12 months because they need longer, e.g. because they had late syphilis or were reinfected.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests