Author's response to reviews

Title: Factors associated with excessively lengthy treatment of tuberculosis in the eastern Paris region of France in 2004.

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Author's response to reviews: see over
Answer to reviewers

Answer to Laura Jean Podewils
Thank you for your comments that greatly helped us to improve our manuscript. We believe that all of them have been addressed and the manuscript was revised accordingly, as detailed below.

Specific comment #1: Authors may consider using “treatment duration according to guidelines” rather than “correct treatment duration” throughout.
We thank you for this suggestion and accordingly, the two following changes were made:
   a) All along the text (i.e. in the second paragraph of the results section), the text "a correct treatment period" was changed to "a treatment duration according to guidelines" (page 7, line 23).
   b) In Table 1, the word "correct" was changed to "according to guidelines"

Specific comment #2: Abstract: - please add the definition used for “excessively lengthy” (e.g., beyond guidelines, with a quick summary of what the guidelines are)
   - add a simple description of the median and range that comprised excessively lengthy treatment
We fully agree with your suggestions, and accordingly, we made the two following modifications in the abstract:
   a) at the end of the subsection Methods, we added the following text for defining excessively lengthy treatment: "According to the guidelines contemporary to the study, excessively long treatment was defined as more than 6-month four drug regimen for thoracic TB with full sensitive strains, and more than 12-month regimen for patients with extrathoracic TB." (page 2, line 8)
   b) The median and range for excessively lengthy treatment was 313 days (range: 214-770, IQR: 272-412). We added the following text in the subsection results of the abstract: "The median duration of excessively long treatment was 313 days (IQR: 272-412)." (page 2, line 19)
Specific comment #3: Authors state they excluded MDR TB cases – were all specimens tested for DST for first-line drugs?

Just want to ensure that some of the patients in the sample were not MDR TB, which might explain excessive treatment if the physician suspected drug resistance.

Thank you for this comment. Indeed, for 9 of the specimens of the patients with excessive treatment, drug susceptibility testing results were not available. Three of these patients had a previous TB and might therefore have a MDR TB. To answer this concern, we performed the statistical analysis, but excluding the nine patients: the results of the multivariate analysis were similar, with the same variables remaining significant. We present below the stata multivariate analysis excluding the nine patients.

| Excessive treatment                        | Odds Ratio | Std. Err. | z      | P>|z| | [95% Confidence Interval] |
|-------------------------------------------|------------|-----------|--------|-----|----------------------------|
| Isolated thoracic TB                      | 2.2        | 0.5       | 3.38   | 0.001 | 1.4 - 3.4                  |
| HIV seropositivity                        | 2.4        | 0.7       | 3.05   | 0.002 | 1.4 - 4.3                  |
| Previous TB                               | 2.7        | 0.9       | 3.14   | 0.002 | 1.5 - 5.2                  |
| Infectious disease specialist prescriber  | 2.1        | 0.5       | 2.91   | 0.004 | 1.3 - 3.4                  |
| Other prescriber                          | 2.0        | 0.6       | 2.32   | 0.021 | 1.1 - 3.5                  |
| 2 institutions per patients               | 1.7        | 0.4       | 2.45   | 0.014 | 1.1 - 2.7                  |
| ≥3 institutions per patients              | 4.5        | 1.9       | 3.49   | 0.0001 | 1.9 - 10.4               |

According to this comment, in the Discussion section, 3rd paragraph, we added the following text:

“In our study, we excluded MDR-TB cases. However, drug susceptibility testing results were not available for nine patients who might therefore be infected with MDR-TB, and explain the analysis results. However, excluding these nine patients yielded similar results with the multivariate analysis, with the same variables remaining significant.” (page 10, line 3)
Specific comment #4: Was there any additional clinical information available along the treatment course (e.g., at 2 months for conversion, 6-month culture result, etc.) that might end itself to clinicians extending treatment? If so, it would be useful to also look at these factors. French guidelines do not recommend performing smear examination along treatment course and French practitioners do not usually perform 2-month culture unless persistence or reappearance of TB symptoms occurs, or in case of MDR-TB. Analysis of the study medical reports confirmed that practitioners did not perform culture control during patient’s follow-up. Therefore, in our study, excessively lengthy treatment cannot be associated with such features.

According to this comment, in the Discussion section, 3rd paragraph, we added the following text:

“Smear examination along treatment course is a potential rationale for performing excessively lengthy treatments. However, French guidelines do not recommend performing and French practitioners do not usually perform 2-months culture unless persistence or reappearance of TB symptoms occurs, or in case of MDR-TB [7]: analysis of the study medical reports confirmed that practitioners did not perform culture control during the follow-up.” (page 10, line 7)

Specific comment #5: Please add a basic description of the median and range (and/or distribution) of treatment duration for “excessively lengthy” treatment
- It would also be useful to see the median, range of treatment duration by a few of the key characteristics (e.g., HIV)

According to a comment of MJ. Van Der Werf, we gathered Table 1, 3 and 4 into a single Table (Table1) in the new manuscript. According to your comment, we added in this new Table 1 a column presenting median treatment duration (and corresponding IQR) for excessively lengthy treatments, according to patients/management characteristics.

Specific comment #6: I would suggest amending the figure to have the box with 478 state “478 patients included in the analysis” (or similar) and then 2 additional boxes below – one with 316 “treatment duration according to guidelines” and the other with 162 “excessively lengthy treatment duration”

We fully agree with your comment and modified Figure 1, according to your suggestions.
Answer to Marieke J van der Werf

Thank you for your comments that greatly helped us to improve our manuscript. We believe that all of them have been addressed and the manuscript was revised accordingly, as detailed below.

**General comments:** The recommendation in the conclusion part of the abstract ‘Better communication among practitioners managing a given patient….’ is not supported by the data provided in the results section. I therefore, suggest to delete this recommendation (or to provide the evidence that supports this recommendation).

We agree with your comment: our recommendation was not supported by the data provided in the results section. Accordingly, and following your suggestion, the last sentence of the abstract in the initial version of the manuscript “Better communication among practitioners managing a given patient is needed to reduce inappropriate lengthy treatment” was deleted. We also deleted the corresponding sentence in the conclusion of the initial manuscript: “Better communication among practitioners managing a given patient is needed, and could be facilitated by computerization of medical reports.”

**Specific comment #1:** The introduction refers to a study on the same subject also performed in France. It is not clear from the introduction why the current study is still needed/valuable if this study already existed.

The study mentioned in the abstract was an evaluation of professional practice throughout an auto-questionnaire. It could therefore not reflect the real practice at the opposite of our retrospective study, which may provide additional information.

“Likewise, a French study comparing actual practices with TB management guidelines showed that patients with extrapulmonary TB were frequently prescribed excessively lengthy treatment.[3]”

was changed to:

“Likewise, a French study based on an auto-questionnaire completed by practitioners compared actual practices with TB management guidelines.[3] These practitioners declared that they frequently prescribed lengthy treatments to patients with extrapulmonary TB.” (page 4, line 5)
Specific comment #2: Please inform the reader whether the French TB treatment guidelines are conform the WHO ones and if not where the deviate.

According to your comment, in the new version of the manuscript, method section, we detailed 2003 international and French guidelines in terms of treatment duration in a subsection “Treatment duration according to international and French guidelines”. Accordingly, the initial text:

“The correct treatment periods were defined as follows, based on the contemporary guidelines: 6 months of a four-drug regimen or of a three-drug regimen including rifampicin, isoniazide and pyrazinamide for patients with fully sensitive strains; 9 months of a three-drug regimen without pyrazinamide; and 6-12 months for patients with extrathoracic TB (i.e. excluding simple pulmonary TB and pleural TB).

In case of resistance to isoniazide, isoniazide was replaced by ethambutol and treatment could be extended to 12 months.

All other patients were considered to have received excessively lengthy therapy.”

was changed to:

“Treatment duration according to international and French guidelines

WHO guidelines contemporary to the study recommended a 6-month four drug regimen for extrapulmonary and pulmonary TB new cases. The corresponding French guidelines specified that treatment duration of extrapulmonary TB should be as long as that for pulmonary TB, but a 9 to 12-month treatment could be proposed for severe extrapulmonary or neuro-meningeal TB. In our study, according to the French guidelines, we considered that a 6-month of four drug regimen for pulmonary-TB and a 6 to 12-month regimen for extrapulmonary TB were in agreement with guidelines. In addition, 6 months of a three-drug regimen including rifampicin, isoniazide and pyrazinamide for patients with fully sensitive strains; 9 months of a three-drug regimen without pyrazinamide were considered to be in agreement to guidelines. In case of resistance to isoniazide, isoniazide was replaced by ethambutol and treatment could be extended to 12 months.

All other patients with no history of previous TB were considered to have received excessively lengthy therapy.

In 2003, WHO recommended an 8-month retreatment regimen with first-line drugs while awaiting drug susceptibility testing (DST) results for patients who had relapsed. In France, DST results being easily available and rates of MDR-TB being low, guidelines recommended starting promptly an empirical therapy with first line drug, waiting for the results of DST: a systematic longer treatment for previously treated patients was not recommended. In our study, according to French guidelines, we considered that a 6-month regimen of standard
treatment was in agreement with guidelines in case of full sensitive strain for previously treated TB cases.” (page 5, line 6)

Specific comment #3: The authors mention that they excluded patients whose treatment period was not known. I did not find the number of patients that was excluded due to this reason in the first part of the results section.
We apologize for our lack of clarity. These patients whose treatment period was not known were included in the 97 patients for whom medical files were not found or incomplete (results, first paragraph, second sentence).
According to this comment, in the Result section, the initial text:
“The medical files of 97 patients (13.4%) could not be found despite an active search”
was changed to:
“The medical files of 97 patients (13.4%) did not include treatment duration follow-up data or could not be found or despite an active search” (page 7, line 14)

Specific comment #4: The authors should mention how they measured socio economic status. Also I did not find the association of socio economic status and excessively long treatment in the results section.
According to your comment, in the new version of the manuscript, Methods section, we made the following modifications:

a) In the Methods section, we added the following text defining precarious situation:
"A precarious socio-economically situation was defined as the absence of health insurance and/or poor living conditions (eg homelessness, migrant shelters, hostels).” (page 6, line 23)
b) The result of the univariate analysis examining the association of socioeconomic status with an excessively long treatment (“OR=1.0 [0.7-1.5], p=0.98”) was added in Table 1 (see also our answer to your comment #11).
c) The study being focused on clinical features (patient and heath institution variables), we suppressed demographic variables from the Table (i.e. age, sex and birth place), and put these data in the text (by the way, none of these variables were associated with an excessively treatment duration). Accordingly, the text “Median age was 36.0 ± 13.5 years, 68% of patients were male and 80% were born abroad.” was added in the Results section. (page 8, line 4)
Specific comment #5: The authors used the student's test for continuous variables. This can only be done if the variables have a normal distribution. I did not find information regarding this in the paper.

We apologize for this statistical term misuse. Indeed, we performed the Wilcoxon-Mann-Whitney non-parametric test for continuous variables and not Student test. According to your comments, we modified last paragraph of the methods part:

"Fisher's exact test was used to identify significant differences between categorical variables, and Student's t test was used for continuous variables."

was changed to:

"Fisher’s exact test was used to identify significant differences between categorical variables, and Wilcoxon-Mann-Whitney test was used for continuous variables." (page 7, line 4).

Specific comment #6: The sentence ‘Infectious diseases specialists are usually aware of published data on HIV sero positive patients’ is not clear. What data on HIV sero positive patients? This sentence also seems to contradict with the sentence that starts with Indeed, a recent retrospective study.

We agree with your comment and accordingly, in the new version of the manuscript, Discussion section, 4th paragraph, the initial text:

"Infectious diseases specialists are usually aware of published data on HIV-seropositive patients [3,8] but often prefer to treat for longer than recommended because they consider their patients more vulnerable, owing to their immunodepression and the fact that they often have disseminated TB."

was changed to:

"WHO 2003, French guidelines and previous studies recommended that TB patients who were living with HIV should have received the same TB treatment duration as HIV-negative patients. [5-7,11] However, specialists of infectious diseases often preferred to treat longer than recommended because they considered their patients more vulnerable, owing to their immunodepression and the relatively high frequency of disseminated TB and severe inflammatory forms. [12]" (page 10, line 15).
Specific comment #7: It is unclear to me what the last section on page 7 has to do with excessive long treatment. I suggest deleting this.

We fully agree with your comment, and according to your suggestion, in the new version of the manuscript, we deleted the corresponding text:

"Moreover, HIV-patients can present unusual inflammatory responses due to a phenomenon of immune reconstitution at HAART initiation, especially when CD4 counts are low. These specific forms can be difficult to treat, might require specific treatment such as corticoids and increase the complexity in management of coinfected patients.[14] A consensus conference is needed to draw up new guidelines for this specific setting.[15]"

Specific comment #8: On page 8 the authors introduce convalescence units and general practitioners. These have not been introduced before. Please also mention these in the methods and results if they are important.

We understand your point, and accordingly, in the new version of the manuscript we made two modifications:

a) in the Methods section, in order to define the number of healthcare institutions involved in patient’s follow-up, the following text was added:

"The number of healthcare institutions by patient was defined by the number of different physicians or health structures involved in patient’s follow-up, e.g. generalist practitioner, hospital department, convalescence unit".(page 6, line 25).

b) in the Discussion section we suppressed the initial text "(hospitals, convalescence units and general practices)" was suppressed.

Specific comment #9: On page 9 the authors mention that patients managed in more than one health care structure may have been lost to follow up. According to the results section none of the eligible patients was lost to follow up (except for those who were not put on treatment). Therefore, I do not understand this statement.

We apologize for our lack of clarity. Indeed, none of the eligible patients were lost to follow-up. According to this remark, we modified the last paragraph of the discussion:

"This study is limited by its retrospective nature and by the fact that some patients managed in more than one healthcare structure may have been lost to follow-up. In addition, some patient files could not be found despite an extensive archive search."
"This study is limited by its retrospective nature, including the fact that some patients were excluded from the study because their files could not be found despite an extensive archive search." (page 12, line 17).

Specific comment #10: How does monitoring the end of treatment have an effect on excessive long treatment? This part of the conclusion is not related to the manuscript. Please explain.

We agree with your comment: the monitoring of the end of treatment cannot have an effect on excessive duration but the monitoring of the duration. We modified the sentence according to this comment:

"A national tuberculosis control program launched in July 2007 aimed at proposing control strategies, in particular at ensuring an adequate management of cases by the monitoring of the end of the treatment"

was changed to:

"A national tuberculosis control program launched in July 2007 aimed at proposing control strategies. In particular the monitoring of the duration of the treatment is expected to result in more adequate treatment durations, according to current guidelines." (page 13, line 12).

Specific comment #11: I suggest making one table of table 1, 3 and 4. Now table 4 is difficult to read because it does not contain numbers.

According to your comment, initial Tables 1, 3 and 4 were gathered in a single Table, Table 1 in the new version of the manuscript. Accordingly, the corresponding text in the Results section was modified.

The initial text:

“The main sociodemographic and clinical characteristics of the 478 patients are summarized in Table 1 according to the treatment duration (normal/excessive). ...

The treatments prescribed for isolated thoracic TB and extrathoracic TB are shown in Table 2 … Table 3 shows the management modalities according to the treatment duration (normal/excessive).”

was changed to:

“Median age was 36.0 ± 13.5 years, 68% of patients were male and 80% were born abroad. The main sociodemographic and clinical and management characteristics of the 478 patients
included in the study are summarized in Table 1 according to the treatment duration (according to guidelines/excessive). ...(page 8, line 4)

The treatment durations for isolated thoracic TB and extrathoracic TB are detailed in Table 2 …”...(page 8, line 12)
Answer to Douglas Fraser Wares
Thank you for your comments that greatly helped us to improve our manuscript. We believe that all of them have been addressed and the manuscript was revised accordingly, as detailed below.

Major Compulsory Revisions
Major comment #1: Results: The authors need to make it clearer to readers what the term “living in precarious conditions” actually means.
According to your comments, we made the two following modifications in the new version of the manuscript:
 a) we added in the abstract (Result subsection) the definition of precarious conditions in the second sentence of results. The initial text:
"48% of patients were living in precarious conditions” was changed to "48% of patients were living in precarious conditions (i.e. poor living conditions and/or no health insurance)" (page 2, line 13)
b) In the section Methods, we added the following text:
"A precarious socio-economically situation was defined as the absence of health insurance and/or poor living conditions (e.g., homelessness, migrant shelters, hostels).” (page 6, line 23)

Major comment #2: In the Abstract, the median age is given as 36.0±15.2 years, whereas in Table 1 it is given as 36±13.5 years. This needs correcting.
We apologize for this inconsistency and have modified the second sentence of the results in the abstract as follows:
The initial text "Median age was 36.0 ± 15.2 years" was changed to "Median age was 36.0 ± 13.5 years" (page 2, line 12)

Major comment #3 Results: Page 5, 4th paragraph, 2nd sentence: In the text, the figure of 104 is given for the total of cases with isolated thoracic TB. However in Table 2, this figure is 114. The authors need to correct this inconsistency.
We sincerely apologize for the inconsistencies in the numbers presented. Univariate and multivariate analyses had been performed with the correct numbers. The correct number of
patients with an isolated thoracic TB and excessively lengthy treatment duration was 107 (as was indicated in initial Table 1). Inconsistencies were mostly due to the 7 patients with isolated thoracic TB and a strain with isoniazide resistance, who were misclassified as having excessive treatment duration. We corrected the inconsistencies both in the results and in Table 2. According to this comment, the following changes were made in the new version of the manuscript:

a) the initial text:
"Among the 279 patients with isolated thoracic TB, 104 (37.3%) had excessively lengthy therapy…"

was changed to:
"Among the 279 patients with isolated thoracic TB, 107 (38.3%) had excessively lengthy therapy…” (page 8, line14)

b) Table 2 was modified with the correct numbers. In particular, a line mentioning the 7 patients with a resistance to isoniazide together with an isolated thoracic TB was added.

Major comment #4 Discussion. 1st paragraph, 1st sentence: The sentence mentions WHO guidelines. However none of the 3 references given refer to WHO guidelines. This needs to be corrected and would suggest that the authors could include the 2010 WHO Treatment Guidelines 4th Edition in the list of references.

We understand your point but we believe that both guidelines published in 2003 (those that were contemporary to the study, and should have guided the management of the study patients) and those published in 2010 (for the discussion section, especially considering the changes for HIV patients with TB) should be mentioned. According to this comment, we made the two following modifications:

a) In the section Methods is first mentioned reference 5 that corresponds to WHO 2003 guidelines. Above all, in the revised manuscript, we detailed 2003 international and French guidelines in terms of treatment duration in a subsection “Treatment duration according to international and French guidelines”. Accordingly, the initial text:

“The correct treatment periods were defined as follows, based on the contemporary guidelines: 6 months of a four-drug regimen or of a three-drug regimen including rifampicin, isoniazide and pyrazinamide for patients with fully sensitive strains; 9 months of a three-drug regimen without pyrazinamide; and 6-12 months for patients with extrathoracic TB (i.e. excluding simple pulmonary TB and pleural TB).[5-7] In case of resistance to isoniazide,
isoniazide was replaced by ethambutol and treatment could be extended to 12 months.[5-7] All other patients were considered to have received excessively lengthy therapy.

As, in practice, treatments rarely last precisely the recommended period, periods of 167-213 days were considered to correspond to six months, 213-274 days to 6-9 months, 274-365 days to 12 months, and 366-543 days to 18 months.”

was changed to:

“Treatment duration according to international and French guidelines

WHO guidelines contemporary to the study recommended a 6-month four drug regimen for extrapulmonary and pulmonary TB new cases.[5,6] The corresponding French guidelines specified that treatment duration of extrapulmonary TB should be as long as that for pulmonary TB, but a 9 to 12-month treatment could be proposed for severe extrapulmonary or neuro-meningeal TB.[7] In our study, according to the French guidelines, we considered that a 6-month of four drug regimen for pulmonary-TB and a 6 to 12-month regimen for extrapulmonary TB were in agreement with guidelines. In addition, 6 months of a three-drug regimen including rifampicin, isoniazide and pyrazinamide for patients with fully sensitive strains; 9 months of a three-drug regimen without pyrazinamide were considered to be in agreement to guidelines. In case of resistance to isoniazide, isoniazide was replaced by ethambutol and treatment could be extended to 12 months.[5-7] All other patients with no history of previous TB were considered to have received excessively lengthy therapy.

In 2003, WHO recommended an 8-month retreatment regimen with first-line drugs while awaiting drug susceptibility testing (DST) results for patients who had relapsed. In France, DST results being easily available and rates of MDR-TB being low, guidelines recommended starting promptly an empirical therapy with first line drug, waiting for the results of DST: a systematic longer treatment for previously treated patients was not recommended. In our study, according to French guidelines, we considered that a 6-month regimen of standard treatment was in agreement with guidelines in case of full sensitive strain for previously treated TB cases.

As, in practice, treatments rarely last precisely the recommended period, periods of 167-213 days were considered to correspond to six months, 213-274 days to 6-9 months, 274-365 days to 12 months, and 366-543 days to 18 months.” (page 5, line 6)

b) In the Discussion section, the part devoted to HIV patients was thoroughly modified. The initial text:

“Infectious diseases specialists are usually aware of published data on HIV-seropositive patients [3,6] but often prefer to treat for longer than recommended because they consider
their patients more vulnerable, owing to their immunodepression and the fact that they often have disseminated TB. Indeed, a recent retrospective study of HIV-seropositive TB patients showed that those receiving a six-month course of treatment had a higher risk of relapse than patients treated for longer periods.[12] Moreover, HIV-patients can present unusual inflammatory responses due to a phenomenon of immune reconstitution at HAART initiation, especially when CD4 counts are low. These specific forms can be difficult to treat, might require specific treatment such as corticoids and increase the complexity in management of coinfected patients.[13] A consensus conference is needed to draw up new guidelines for this specific setting.[14]

was changed to:

“WHO 2003, French guidelines and previous studies recommended that TB patients who were living with HIV should have received the same TB treatment duration as HIV-negative patients.[5-7,11] However, specialists of infectious diseases often preferred to treat longer than recommended because they considered their patients more vulnerable, owing to their immunodepression and the relatively high frequency of disseminated TB and severe inflammatory forms.[12] A recent retrospective study of HIV-seropositive TB patients showed that those receiving a six-month course of treatment had a higher risk of relapse than patients treated for longer periods.[13] It’s worth to mention that the current 2010 WHO guidelines specify that some experts recommend prolonging TB treatment in persons living with HIV.[14] Therefore, the more likely excessively long treatment of HIV patients in our study probably reflects the evolution of practice and guidelines.”(page 10, line 15)

Major comment #5: 2nd paragraph, 1st sentence: Is it appropriate here to use a reference which reports on the treatment of latent TB infection, when discussing excessively long treatment of active disease?
We agree with your comment and accordingly, in the new version of the manuscript, the initial text: "Although cost-effectiveness studies of different treatment durations have only been conducted for latent TB,[11] excessively long treatment of TB disease is likely to be more costly but not more effective." was suppressed.

Major comment #6: 2nd paragraph, 2nd sentence: However although longer treatment may be more costly, there is evidence, especially in HIV-associated TB, that this may result in lower rates of relapse. This the authors themselves state in the 3rd paragraph on the same page.
We agree with your comment. See our answer to your comment #4 (modification b) for the modifications made.

Major comment #7: 4th paragraph, 1st sentence: Authors need to consider that most treatment guidelines issued recommend longer than 6 months of treatment for previously treated patients.
We agree with your comment, previously treated patients have a higher likelihood of drug resistance. As indicated in our answer (modification a) to your comment #4 we now detail treatment guidelines including a special mention for previously treated patients.

Major comment #8: 4th paragraph, 4th sentence: The authors discuss about French guidelines in the sentence, whereas the reference 5. refers to the ATS guidelines. This needs amending by the authors.
We apologize for this error and in the revised version of the manuscript, we corrected this reference.

Major comment #9. Table 1: Inconsistencies in figures between Tables 1 and 2 need to be corrected by the authors. Total for “Excessive” is 162 in Table 1 but 169 in Table 2. Figures for Isolated thoracic TB “Correct” is 172 in Table 1 but 165 in Table 2. And for “Excessive” 107 in Table 1, but 114 in Table 2.
Table 3: Is the term “.. according to management modalities” the most appropriate phrase?
Total for “Excessive” is given as 162 in Table 3, but 169 in Table 2.
We sincerely apologize for these inconsistencies due to the 7 patients with isolated thoracic TB and a strain with isoniazide resistance, who were misclassified as having excessive treatment duration (see our answer to your comment #3). According to this comment, we corrected these inconsistencies in the Tables of the revised version of the manuscript.

Major comment #10: The meaning of “Number of structures per patient” is unclear and needs making clearer for the reader’s better understanding.
We apologize for our lack of clarity. According to your comment, in the new version of the
manuscript we made two modifications:
a) in the Methods section, in order to define the number of healthcare institutions involved in patient’s follow-up, the following text was added:
"The number of healthcare institutions by patient was defined by the number of different physicians or health structures involved in patient’s follow-up, e.g. generalist practitioner, hospital department, convalescence unit". (page 6, line 25)
b) in the Discussion section we suppressed the initial text “(hospitals, convalescence units and general practices)” was suppressed.

Minor essential revisions
Minor essential revisions #1: 7th paragraph, 1st sentence: Suggest that authors amend the term “…in a weakly endemic country..” to “in a low incident country” or “.low prevalent country”.
Thank you for your suggestion. Accordingly, the term "in a weakly endemic country" was changed to "in a low incident country". (page 12, line 11)

Minor essential revisions #2. 8th paragraph, 3rd sentence: Suggest amending the term “..that declare..” to “..that notify..”.
Thank you for your suggestion. Accordingly, the term "that declare" was changed to "that notify".(page 12, line 23)

Minor essential revisions #3: 8th paragraph, 6th sentence: The meaning of this sentence is somewhat unclear and the authors need to make the sentence clearer for the reader.
According to your comments, the initial sentence: "Finally, links between excessively long treatment and certain management modalities, such as the use of computerized follow-up, may have been overlooked, owing to a lack of statistical power." was deleted.
Answer to Denise Silva

Discretionary revisions #1- I suggest to provide the odds ratio and p value for alcoholism and injecting drug use in multivariate analysis (Table 4), although the were not significant.

Thank you for your comment, we understand your concern. As precised in the Method section, we performed a multivariate analysis, including all variables with p values $\leq 0.20$ in univariate analysis with backward elimination of the non significant variables. This is usual way of performing such a multivariate analysis. Therefore, we cannot provide values for the final model including alcoholism and injection drug variables since these variables were eliminated during the backward procedure. When included in the model, these two variables respectively resulted (just before their elimination) in the following odds ratios (estimate, p value, [95% confidence interval]): 1.4, $p < 0.26$, [0.8-2.4] and 2.8, $p < 0.21$, [0.6-14.6].