Author’s response to reviews

Title: Timing of treatment interruption among latently infected tuberculosis cases treated with a nine-month course of daily isoniazid: findings from a time to event analysis

Authors:

Marie Seraphin (nseraphin@ufl.edu)
HsiaoChu Hsu (stray0227@gmail.com)
Helena Chapman (Helena.chapman@medicine.ufl.edu)
Joanne Li (joanne.li@medicine.ufl.edu)
Lori Johnston (Lori.Johnston@flhealth.gov)
Yang Yang (yangyang@ufl.edu)
Michael Lauzardo (mike.lauzardo@medicine.ufl.edu)

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RE: PUBH-D-19-01094

Title: Timing of treatment interruption among latently infected tuberculosis cases treated with a nine-month course of daily isoniazid: findings from a time to event analysis

Response to Reviewers

Authors General Response: We thank the editor and the two reviewers for their thoughtful comments on our work and the suggestions for improvement. Our specific responses to the reviewers are included below. We also edited the manuscript and associated files to meet BMC Public Health style requirements.

REVIEWER # 1 – Lisa Ronald

1. The data were obtained from LTBI registry data pooled across 67 county health units. Additional information about the LTBI registry in the methods section would be helpful. Does the catchment population for these data cover all of the health units in Florida, and how complete
is this registry likely to be for LTBI testing and treatment information for the catchment population? Is there mandatory reporting for LTBI testing and treatment to the health units? Additionally, where were the treatment outcomes definitions were obtained from, ie. was treatment completed, lost-to-follow-up, etc. a clinician-defined outcome within the registry? Also, it would be helpful to provide a comment in the methods section that data are not available regarding drug dispensation—this is mentioned later in the limitations section, but it would be helpful to have this mentioned earlier.

Authors Response: The catchment population for these data cover all the health units in Florida. Latent tuberculosis infection (LTBI), unlike active tuberculosis (TB) is not a reportable condition in Florida so reporting to the health units is not mandatory. As such, the data presented here do not capture people who were diagnosed and treated in the community by their primary care providers or other community health clinics. However, we believe this population is small, as LTBI is largely managed by Health Departments in Florida. In addition, private and community providers invariably refer clients to the health unit in their county of residence to follow-up on positive LTBI test results. Clients referred with a positive test (TST, and/or IGRA) are evaluated by health department providers and offered therapy if LTBI diagnosis is confirmed. We have revised lines 114 – 126 as follows:

Data from a LTBI treatment registry collected from 2009 to 2015 were pooled for these analyses. Persons with LTBI were diagnosed and managed locally by the 67 different county health departments in Florida, and the Florida Department of Health TB Control Program pooled the data centrally. LTBI diagnosis was based on either a positive tuberculosis skin test (TST) and/or interferon gamma release assay (IGRA) test followed by a medical evaluation and additional testing consisting of chest x-ray and, in some cases, acid-fast sputum smear examination to rule out active TB disease. We included everyone initiated on INH in the analysis. Patients were prescribed self-administered INH 300 mg per kg body weight daily, for nine months. Drugs were dispensed during scheduled monthly visits to the health department LTBI clinic. LTBI is not a reportable condition in Florida. As such these data only capture people diagnosed and managed by county health department tuberculosis clinics in Florida.

The treatment outcomes (i.e. treatment completed, lost-to-follow up, decide to stop, adverse reaction, died) are defined by a TB nurse or doctor involved in the care of the LTBI client at the health unit level using standardized terminology and were available within the registry. We added this sentence (lines 128 – 129) “All treatment outcomes were available within the registry and recorded at the health department level by a provider involved in the care of the LTBI client” to further clarify in the methods section.

We know from the data that drugs are dispensed during scheduled monthly visits to the health department TB clinic. We added this detail in lines 119 – 120. However, because treatment is self-administered and clients are not required to bring back pill bottles for pill count, additional information that would allow us to more accurately define the timing of treatment default is not
available. For example, a patient is recorded as lost to follow-up by the health unit only after they have missed their scheduled appointment. It is likely that this patient actually never took any of the monthly supply of pills or decided to stop days before. It is one of the points we make in this paper. We have edited the limitations section (lines 284-288) to reflect this point.

2. The reported prevalence %'s for some of the risk factors (diabetes, immuno-suppression) seems low. Is the co-morbidity risk factor data in this registry self-reported or clinician-reported, and is there any indication about how complete the risk factor data is? This may warrant further discussion in the limitations section.

Authors Response: The co-morbidity risk factor data for HIV and diabetes are self-reported in the LTBI registry. Clients are offered an HIV test, if they do not already know their HIV status but they can opt out. The other co-morbidity risk factors, i.e. chronic renal failure, corticosteroid therapy, hematologic disorders, are clinician reported. To get a sense of the completeness of the risk factor data, we compared the prevalence in a tuberculosis registry collected 2009 – 2015. Active tuberculosis is reportable by statute in the State of Florida. In addition, the TB program reports all cases to the Centers for Disease Control and Prevention (CDC), using a report of verified case of tuberculosis (RVCT). In that population of 4,911 TB cases, HIV prevalence is 12.7% and the prevalence of diabetes is 11.7%. This suggests these two co-morbidity risk factors are underreported in the LTBI dataset. We have added lines 295-309 in the discussion section to expand on this limitation to the data.

In addition. The co-morbidity risk factor data evaluated in this study, such as HIV co-infection and diabetes, are self-reported and likely suffer from underreporting bias. To evaluate the completeness of the data, we compare the prevalence of these two risk factors in a TB registry collected 2009 – 2015. TB is reportable by statute in the State of Florida [40]. In addition, the TB program reports all cases to the Centers for Disease Control and Prevention (CDC), using a report of verified case of tuberculosis (RVCT) [41]. In that population of 4,911 TB cases, HIV prevalence is 12.7% and the prevalence of diabetes is 11.7%. These results suggest that these two co-morbidity risk factors are underreported in the LTBI dataset. In addition, it is possible that LTBI clients with HIV and diabetes are managed in the community by their primary care providers and are not reported to their home county health departments, since LTBI is not reportable in Florida.

3. Did the authors have any data regarding age? It would have been interesting to see how the outcomes differed across age groups (particularly completion and adverse event frequencies in older age groups).

Authors Response: The age at LTBI classification is recorded for all cases in the dataset. However, we used age to classify the study population into three groups: pediatric (ages 0 – 17 years), close contact to an infectious case and other adults (both excluding clients 0-17 years of
Because we used age in defining the three groups, we did not evaluate age effect within any single group. We know from the literature and practice in our settings that children and recent contacts are prioritize for LTBI therapy, independent of other clinical and sociodemographic risk factors for progression to active disease. By creating these three groups, we can see from our results that indeed pediatrics and recent contacts have a higher prevalence of treatment completion (52.0% and 55.6%, respectively), despite representing only 25.2% and 13.0% of the total study population. Initially, we conducted the analyses looking at the association of outcomes with age categories and the results were not as informative as they are now.

4. The authors excluded a large number of people from the analysis (almost 40% of people listed as initiating INH therapy were excluded from the analysis, with 23% excluded due to missing treatment start date and 13% with a medical plan open for more than 9 months). Some LTBI treatment guidelines identify treatment completion as 240 doses within 12 months. Did the authors do any sensitivity analyses to test the impact of an expanded time window regarding treatment completion, and whether inclusion of people with a treatment plan open for >9 months changed the conclusions? I understand that this was a time-to-event analysis, but would extension of the window to 12 months as a sensitivity capture most of these excluded people?

Authors Response: We reanalyzed our data and modified figure 1 – the sample selection flowchart. The initial organization of the flowchart misleadingly suggested that cases candidate for treatment were excluded from the analyses. We used a stepwise method to exclude cases, separating the cases who refused LTBI therapy from those who were not candidate for LTBI therapy either because of history of TB disease, prior LTBI therapy, or pregnancy. At the suggestion of the reviewer, we revised our criteria to exclude those who completed therapy in under 6 months (likely window prophylaxis until TB disease is ruled out and/or recording errors) and those with a treatment medical plan extending beyond 12 months, independent of treatment outcome, changing the follow-up period from 9 to 12 months. These revisions mean that now the study population is composed of 12,495 LTBI cases, instead of the 9,229 cases initially reported. Also, extension of the study window from 9 to 12 months did not change the overall findings.

Overall, of the 18,294 with a positive TST or IGRA from 2009 – 2015, 17,587 were eligible for therapy, 17,290 accepted treatment, and 14,359 were offered INH daily for nine months. We determined 829 were duplicate records using a combination of SAS/SQL and manual screening. Overall, we had 13,530 cases included in the study before any exclusion.

We excluded 516 who completed treatment in under six months, and 519 with a treatment medical plan opened for longer than 12 months. The total eligible cases excluded is 1,383 or 7.6% of the study sample. Of the 519 excluded due to a treatment plan opened longer than 12 months, 332 (64.0) eventually completed therapy within a minimum of 370 days and a maximum of 2058 days. Obviously, some of these observations include a combination of people who indeed had intermittent treatment compliance issues throughout therapy as well as data quality issues.
Because we could not differentiate between the two, we decided to exclude this group altogether from the analyses. We looked at a frequency distribution graph of the data before we excluded these cases (Figure S2A) and after exclusion (Figure S2B) and notice that the overall time distribution of the treatment outcomes did not change. This leads us to conclude that the observations excluded were more likely outliers and did not significantly bias the overall study results. We have added lines (169–173) to that effect.

5. Re: Figure 1, there are a reported 19,726 people testing positive for TST and/or IGRA and of these, 15,602 are listed as initiating INH therapy. Figure 1 shows that 992 never initiated treatment, what about the other 3,132 who were candidates for INH therapy but didn't initiate treatment? Also a suggestion for Figure 1- if the authors can add an additional final box with # completing treatment, it would make the LTBI care cascade data clearer (# eligible, # initiating, and # completing).

Authors Response: Please see our answer to question 4 above explaining modifications to Figure 1. We have also added a box with the number completing treatment, using the treatment outcome recorded in the medical record.

REVIEWER # 2 – Joseph Puyat

1) The authors should clarify what they mean by this statement: "On average, patients defaulted on their prescribed nine-month daily INH therapy within the first month..." The data do not seem to support this statement.

Authors Response: We mean that most clients who defaulted on the nine month therapy did so within the first 30 days. With the recommended changes to the exclusion and inclusion criteria (please see reviewer 1 comments above) and additional results included in supplement (Figure S2), we can clearly see the big drop in treatment compliance that occurs around the first month of therapy. Something interesting these time distribution graphs show is that past the initial two months, people who are indeed going to complete therapy do so. Our risk factor data support that people who remain compliant are indeed at high risk for progression to active disease and are thus motivated to complete therapy. This is one of the points we make in the discussion; the need for more effective risk communication when prescribing LTBI therapy, independent of how long the treatment will last. The shortest LTBI therapy currently available last three months, which is still longer than the average time to treatment default observed in this study.

2) The numbers mentioned in the text and on Figure 1 do not add up. From 19,726 a total of 992 who never initiated treatment were excluded. There should have been 18,736 in the next box but only 15,602 were shown. What happened to the ~3,000?
Authors Response: We have modified the text and Figure 1. Please see our response to reviewer 1 question 4 above for more details. From 2009 -2015, 18,294 clients had a positive TST or IGRA. We excluded the ones not eligible for LTBI therapy, leaving a total of 17,587 eligible clients. Of those, 297 refused treatment; of the total who accepted LTBI therapy (n=17,290), 14,359 were offered INH. The other 2,931 were offered other regimen, such as 4 months rifampicin or 3 months INH and rifapentine. These numbers are relatively small compared to the bulk of clients offered INH, as these shorter regimen are newly available in Florida.

3) How were patients lost to follow-up differentiated from patients who chose to stop?

Authors Response: These outcomes were recorded by the medical provider in the client record. Clients coded as “chose to stop” made that request directly to the provider, whereas, those coded as lost to follow-up did not return to the clinic, and could not be reached by the health unit when contacted.

4) What is the rationale for considering losses at follow up as treatment default. Why are these events not right-censored?

Authors Response: The nine month INH therapy is dispensed at monthly intervals. Clients need to come back to the clinic to pick up their next monthly supply and also be medically evaluated if adverse reactions to the treatment. We coded losses at follow up in the context of this study as observed default time because if the client did not come back for their next month drug dispensation, it signifies they defaulted on therapy. These clients can come back, and depending on when they do, they may continue the regimen but the duration is extended or they are initiated on a new treatment plan.

5) Are adverse reactions and deaths constitute competing risks? If yes, why didn't the authors analyze these events as such?

Authors Response: We initially considered whether adverse reactions and deaths should constitute competing risks, and then decided against it. The most serious adverse reaction associated with INH monotherapy is hepatotoxicity and it is extremely rare (1 – 4% of clients) and occurs within the first few months of initiating therapy. In our study, about 2% of patients had adverse reaction (Table 1) and most did so indeed in the first few months of initiating therapy (Figure S2). In these cases, the provider will stop the INH and evaluate whether to switch the client to a different drug, in which case the client would default on INH therapy; or reattempt INH monotherapy after a washout period, in which case the treatment outcome would be recorded in the medical record. We did not consider death a competing risk because clients eligible for LTBI therapy are not at risk of dying from LTBI itself nor the treatment.
6) Did any of the status pertaining to HIV, diabetes and other immune suppressive conditions change during follow-up? If yes, why they were not examined as time-dependent variables.

Authors Response: The clinical risk factors, HIV, diabetes and other immune suppressive conditions, were collected at one time point at baseline to determine eligibility for treatment among other risk factors. They were not reassessed during treatment. In addition, we do not believe, these health conditions change during the 6-12 month treatment follow up period.

7) There were a large number of patients excluded from the analyses. The authors did say (on the first paragraph of the Results section) that many of these excluded patients eventually completed therapy. Because of this, I would encourage the authors to examine more thoughtfully these exclusions as they could change the manuscript's key findings. For example, the statement on the abstract that: "Overall, 47.9% failed to complete therapy" is misleading as this appears to pertain only to about half of the total patients that could have been examined. Given these issues, I would hold off on interpreting or reading the rest of the results presented by the authors.

Authors Response: please see our response to reviewer 1 comment #4. We have revised the exclusion criteria and extended the treatment follow-up period from 9 to 12 months. Indeed, most TB programs consider INH treatment completion as 270 doses within 12 months of therapy. With these revisions and others to the study sample selection, we now have a total study population of 12,495 instead of the 9,229 initially included. In addition, the total eligible clients excluded from the analyses is now 1,035 or 7.6%. Half of the excluded cases was due to individuals on therapy longer than 12 months – beyond the recommended treatment protocol or even the study follow up period. Of that group, a little over half (n=333) eventually completed therapy. We believe time itself presents a competing risk to treatment default in this subsample and this subset would have more appropriately been analyzed using competing risk criteria; however, the moments of defaults could not be distinguished from the moments of treatment compliance. We have added Figure S2 comparing the time distribution of different treatment outcomes before and after exclusion of the 1,035 cases and we can see that the overall study follow up time distribution did not change, suggesting that these cases were likely outliers and or indication of data recording issues in the medical record. In addition, even after the changes to the exclusion and follow up duration, the overall study findings did not change – 49.6% of the total sample was recorded to have completed therapy, 25.0% were loss to follow-up and 23.4% chose to stop therapy for an overall treatment default rate of 48.4% (Table 1).

8) Figure 2 was hard to interpret. The y-axis should either say 0 to 100% or 0 to 1.00, not both. Also, I'm not sure if the authors are trying to show treatment discontinuation and not treatment completion in these plots. As they are, the plots suggest that during the weeks before the fourth, 100% of the patients have completed treatment, which is not correct. Perhaps what the authors meant was that during the weeks before the fourth, all of the patients they examined have not discontinued treatment.
Authors Response: We have edited the plot y-axis. We have also changed the scale of the x-axis to show days instead of weeks. These plots show the probability of completing therapy (i.e. staying on treatment for 6-12 months), with the drops in the curves pinpointing specific time points when clients defaulted (i.e. lost to follow up or chose to stop). In other words, what the plots show is the percentage of patients examined who prior to their next scheduled visit to the LTBI clinic to pick up more drugs (every 30 days) had not discontinued therapy. In the manuscript we report the inverse of that, which is the proportion who indeed defaulted. This results are supported by the distribution of time to treatment outcomes (figure S2) where most of the default events are recorded within the first 30 days of treatment initiation. The first 30 days post treatment initiation is the time we think that most patients just do not return to the clinic, but the clinic staff only record the treatment outcome only after the client has missed the appointment. The point we make in the paper is that it is very likely that the client actually never took any of the first month supply of drugs. We edited the result section (lines 204 – 226) to include these changes.

9) The authors mentioned in the text (and I think showed in Figure 2, as well) that the median time to treatment discontinuation was around 40 weeks. This is not possible if the authors excluded everyone with more than 9 months (~40 weeks) of treatment. I'd encourage the authors to review the design of their study and their data analysis.

Authors Response: We have revised the exclusion criteria for the study to keep cases on treatment for a maximum of 12 months and ran all analyses again. We are now presenting the time to treatment interruption in days, instead of weeks, since therapy is daily. The median time to treatment completion is 306 days. This way of presenting the data is counterintuitive; however, what it really boils down to is that on average the study sample is on treatment for 306 days, i.e. enough doses to complete therapy.

10) Last, I would have appreciated more discussion of the authors' results. Most of the information contained in the discussion, while interesting, do not seem to be directly relevant to the study's key findings.

Authors Response: One of the key findings of the study is that INH treatment default is common; almost half of the people initiated on therapy did not complete. We also show that default occurs early in therapy, with almost 20% of cases defaulting in the first 30 days of initiating therapy. In the discussion we talk about ways health departments could increase treatment adherence. We also argue that if more patient-centered approaches are not implemented, maybe treatment adherence will be poor, independent of the length of therapy. With this revision, we have added additional texts around underreporting of some of the risk factors evaluated in this study (i.e. HIV, diabetes).