Determinants of treatment outcomes of multidrug-resistant tuberculosis (MDR-TB): an Individual Patient Data (IPD) Meta-Analysis - Update

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Introduction

Multidrug-resistant tuberculosis (MDR-TB), defined as tuberculosis resistant to at least isoniazid (INH) and rifampin (RIF), has become a major threat to global tuberculosis control in recent years.

In 2009, WHO issued a call for evidence to draft new recommendations for treatment of MDR-TB. Initially, 3 systematic reviews were completed and meta-analyzed the data of eligible literatures [1-3]. However, identification of optimal treatment regimens was extremely difficult as pooling of results across studies was limited by the complexity of the patients’ characteristics and individualized treatment. To address this problem, the McGill group (led by Dr. Dick Menzies) conducted an individual patient data (IPD) study in 2010, and a data base was assembled of individual patient records from almost 10,000 MDR-TB patients from 32 centers of 20 countries. Data for each patient include age, gender, history of prior therapy, AFB smear, chest x-ray findings, HIV co-infection, drug sensitivity test results, detailed TB therapy given and treatment outcomes [4].

This rich data base has allowed seven distinct set of analyses to address different important questions regarding interpretation of DST, role of surgery, prognosis and correlates of treatment success of MDR-TB. Meta-analysis of this data set produced the majority of evidence which the WHO expert committee used to make new recommendations for MDR-TB treatment published in 2011 [5]. Five papers (one in PLoS Medicine, two in ERJ, and two in CID) have been published so far and the results have influenced several sets of WHO recommendations [4, 6-9].

In 2015, WHO planned to update their recommendations of MDR-TB treatment. An updated systematic review and aggregate data meta-analysis of recent MDR-TB publications (Jan. 2009 – Sept. 2015) was conducted by the McGill group. However, although 74 eligible articles were identified, the differences in regimens used, plus individualized approach to treatment in majority of the studies made pooling the data difficult, and severely limited inferences based on the findings regarding drug efficacy and drug safety. Given this, the McGill group in collaboration with the US Centers for Disease Control and Prevention (CDC) and American Thoracic Society (ATS) will conduct an updated IPD study in order to generate evidence to update the ATS/CDC/IDSA MDR-TB treatment recommendations. Authors of eligible publications from Jan. 2009 will be contacted and asked for participation in this study. An updated data base will be assembled and individual patient data will be analyzed to address major questions regarding MDR-TB treatment.
**Objectives**

Conduct an updated individual patient data (IPD) meta-analysis of patients who were treated for MDR-TB to determine treatment correlates with treatment outcomes.

The primary outcome assessed will be:

1) End-of-treatment outcomes of cure/completion, failure (& relapse if measured), death, and non-completion (formerly known as default). These will be defined by Laserson et al., 2005 [10].

Additional outcomes assessed will be:

2) 6-month culture conversion

3) Serious adverse events (defined as Grade 3-4 events, or defined operationally as drugs discontinued permanently)

We will have a particular focus on certain drugs, for which we believe there is significant new evidence from recently published studies:

- High-dose isoniazid (INH)
- Later generation fluoroquinolone (FQN)
- Linezolid
- Clofazimine (unclear how much new data on Clofazimine outside of the short regimens)
- Bedaquiline & delamanid (Most of this data is likely to be from recent randomized trials, but it is unclear if that data will be available.)
- Carbapenems (recent publications on ertapenem, imipenem and meropenem)

**Methods**

1. Study inclusion criteria

   a. Original articles published since January 2009 in peer-reviewed / indexed journals

      We will include all eligible articles published since January 2009 in peer-reviewed / indexed journals. Additionally, as this IPD will be an update of the prior IPD conducted in 2010, we will contact all authors that participated in the 2010 IPD – to ask if they can add new data from patients treated more recently at their centres. We will not attempt to contact authors of studies that were eligible for prior IPD (studies published prior to Jan. 2009), who did not respond or refused to participate previously. The characteristics of patients and treatment outcomes included in the 2010 IPD were not significantly different from the characteristics of patients in the studies not included [4].

   b. Confirmed MDR-TB

      MDR-TB disease should be bacteriologic confirmed (phenotypic or genotypic)

   c. Patients with bacteriologically confirmed pulmonary disease

      Our analysis will mainly focus on the data of patients with pulmonary diseases. Information on treatment outcomes in patients with extra pulmonary (EP) MDR-TB could be a secondary objective for later analysis. This is because outcomes are less certain. We will gather information on EP forms, with a particular effort to analyze TB meningitis, and disseminated/miliary TB. Authors will be asked for detailed data on diagnostic methods and outcomes.
d. Adults
We will include studies of adult patients (age definition may vary but at minimum age ≥ 12). Studies that have both children and adults will also be included (primary analysis will exclude the children). A pediatric IPD has just been completed; it may be interesting to merge these later, to perform one analysis with greater power.

e. At least 25 patients with MDR-TB
We will include studies that have at least 25 patients with MDR-TB.

f. Must report at least one of the following outcomes
(1) End-of-treatment outcomes: Cure or complete (success) vs Fail or relapse or died. The minimal requirement is that the study reported at least success vs fail/relapse, or success vs death. We would also ask for information on default/lost and acquired drug resistance but studies not reporting these could be included.
(2) 6-month sputum culture conversion. (If an article only reported time to culture conversion or conversion at other time points, the authors will still be contacted to ask if information of any of the three IPD study outcomes listed here are available. If no outcomes of interest are available, the study will be excluded)
(3) Adverse events (AE). In the 74 recent studies already reviewed, there was tremendous heterogeneity in the methods of AE definition, documentation, and reporting. However, as AE is a very important outcome, we will ask for the AE data, but it may take more time and effort to analyze these data. Thus, this should be a secondary outcome to avoid delays in reporting the most important outcomes.

2. Study exclusion criteria
a. Exclude “grey literature”
Studies published only as grey literature will be excluded (otherwise unpublished studies are generally of very poor quality, or the authors are still trying to publish. In the latter case, most don’t want to send their data until they publish).

b. MDR regimen of less than 12 months.
Papers describing the results of treatment with regimens of less than 12 months will not be included. If a study compared long-course with short-course MDR treatment, we will include data from the long-course cohort (standard 18-24 months treatment). An IPD data set exclusively of patients treated with the short regimens has just been assembled. It would be interesting to combine this later, but that data set is still preliminary and several investigators that contributed data still want to publish their own results. Hence it is unlikely that these data will be available in the next 6 months. When available, combining the data sets would be of interest, to allow comparison of outcomes with the short regimens and the longer, more conventional regimens.
3. Variables to include in IPD
(Note: these are to be considered minimum criteria for all studies. If studies have more information, the additional information should be added into the data base, allowing analysis in a sub-set of studies that reported more details. Authors will be asked for data on all outcomes.)

a. Base line characteristics
Minimum criteria: age, sex, HIV status (and ARV treatment if HIV positive), prior treatment with first line or second line TB drugs, AFB sputum smear, chest X-ray findings, and site of disease (pulmonary or extra pulmonary, and site if extra pulmonary).
Additional: Information on weight, BMI, diabetes, cigarette smoking and alcohol consumption will be asked for, but would not be considered minimum criteria (i.e. studies will not be excluded on this basis)

b. Drug sensitivity testing
Results of all phenotypic and/or genotypic tests will be requested.
Minimum criteria: Pre-treatment DST for all 4 first line drugs (if DST for EMB and PZA is not available – these studies may be included, if all other criteria met). Also DST to at least one FQN, and at least one second line injectable (in order to account for XDR and pre-XDR in the analyses). Date of specimen collection relative to treatment start dates. (We may consider studies that performed only molecular tests in lieu of phenotypic results, but then results of INH & RIF testing must be available)

c. Treatment
Minimum criteria: Drugs used (at least 1 month) in the initial phase, and (separately) in the continuation phase; duration of each phase in months
If resectional surgery performed then additional details would include timing, type of resection, and relationship to sputum conversion.
Ideal: Specific dates of start and stop, and doses for each drug used for each patient. This would include drugs used before diagnosis of MDR-TB confirmed.
Studies with more detailed treatment information can be included (e.g. PETTS, and TBESC Task Order 28 of MDR outcomes in the United States 2005-2007). This sub-set of studies may provide added information.

4. Site Questionnaires
Authors/contributors for each participating site would also fill out a “site questionnaire” regarding laboratory methods for AFB smear, culture, and DST, and the DST critical concentrations used to define resistance. They would be asked for information on usual mg/kg dosing of drugs for all drugs used, and definition for all outcomes used – including end-of-treatment outcomes, adverse events, and sputum conversion.
5. Procedures to identify and select eligible studies for the IPD

a. Study selection from systematic reviews

From August to November 2015, a systematic review was conducted by investigators at McGill University to identify studies published since Jan. 2009 of treatment of MDR-TB (including XDR-TB). See Annex 1 for detailed search strategy, study selection criteria, and procedures and methods of data extraction and analysis. See Annex 2 for details of studies selected. This review was completed, and results have been presented at a meeting of an expert committee for MDR-TB treatment – held in Geneva Nov. 9-11, 2015. Some additional analyses are ongoing to clarify issues raised at that meeting.

In 2015, another systematic review was conducted independently by investigators from CDC (Atlanta) and ATS to identify studies published since January 1989 of treatment of MDR-TB. (Detailed search strategy, study selection criteria and procedures, as well as Prisma diagram of study selection to date to be sent). This CDC/ATS review has been completed up to a selection of (600) full texts for review.

In addition, since Jan. 2009, there have been at least 4 systematic reviews published of: Treatment with Linezolid, Clofazimine, Cycloserine/Terizidone, and Amoxy-CLV or Macrolides. We will search for all systematic reviews of MDR-TB treatment published since 2009. The reference lists of these reviews will also be searched, and any studies published since Jan. 2009 will be potentially eligible. These titles will be added to the 600 titles selected for full text review in the 2nd review.

We will consider all studies included in the McGill review, to be eligible for the IPD. To identify any additional studies, we will first restrict the list of titles selected for full text review from the CDC/ATS review (plus systematic reviews as above) to titles of studies published since Jan. 1, 2009. This list will be compared with the list of full texts selected from the McGill review. Any full texts not appearing on the McGill list will be reviewed (full text) by two reviewers working independently to decide if eligible for the IPD.

Finally, we will write to all authors of the 31 studies included in the 2009 IPD, to ask them if they have new data that could be added. If so, this will be added (same eligibility criteria will be applied – minimum 25 patients with microbiologically confirmed pulmonary MDR-TB, etc.)

b. Studies eligible for inclusion in this IPD

The study selection procedure above will give us a final list of studies eligible for the IPD. We will write to all corresponding authors of these studies – to ask their participation. Studies considered eligible to be included in this IPD will be:
- Studies of MDR patients selected by the process described above
- Authors agree to send data (and send it!)
- Data meet minimum criteria as described above

6. Ethics:

Ethics approval for the IPD has been maintained at McGill since 2009. This will require a protocol amendment. This protocol will also require approval at CDC. All data sent by authors will be non-nominal, and patients will not be contacted directly, so there should not be any ethical issues. Ethics approval may be needed at participating sites – this will be left to each site to determine.
7. Activities

(1) Send to all authors of eligible studies a letter explaining the study, the study protocol, and a memo of understanding, inviting their participation. If the creation of the IPD is motivated by the development of guidelines this could generate greater enthusiasm. The tight timelines for the guidelines development may help add some time pressure to authors (who can be very slow to send data).

(2) Collect the data sets from the individual centers and begin the work of understanding the variables and sorting through each data set; this requires at least a month, because frequent e-mails are needed back and forth to the authors to clarify many issues. It would be important to ask each author for a data dictionary as well.

(3) Analysing the data.

Timeline

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Activity</th>
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<tbody>
<tr>
<td>Early January, 2016</td>
<td>Complete protocol and letter of agreement (MOU) with sites</td>
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<tr>
<td>Mid-January, 2016</td>
<td>Ethics approval – McGill and CDC; complete study selection</td>
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<tr>
<td>Late January, 2016</td>
<td>Initial letters to all authors</td>
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<tr>
<td>By the end of April, 2016</td>
<td>Gather data from all participating sites</td>
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<tr>
<td>February to early June, 2016</td>
<td>Data cleaning, variable transformation, creation of merged data set</td>
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<tr>
<td>June – August, 2016</td>
<td>IPD meta-analysis</td>
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<td>At a later stage</td>
<td>We may add other IPD sets – the older dataset (assembled in 2010), pediatric IPD (from 2015), and the Short regimen IPD (assembled in Nov. 2015). These would provide added power to examine certain drugs (e.g. high dose INH), and provide a basis for comparison (e.g. the short regimen)</td>
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<tr>
<td>By September, 2016</td>
<td>Preliminary report submission – to all authors and to CDC/ATS</td>
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Reference


