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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.  
Project Funding Source: National Institute of Allergy and Infectious Diseases at the U.S. National Institutes of Health (grant number K08 AI141740)  
How did you learn about the YODA Project?: Colleague  

Conflict of Interest


Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be
used to support litigious/commercial aims.

**Data Use Agreement Training:** As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. **NCT00449644 - A Phase II, Placebo-controlled, Double-blind, Randomized Trial to Evaluate the Anti-bacterial Activity, Safety, and Tolerability of TMC207 in Subjects With Newly Diagnosed Sputum Smear-positive Pulmonary Infection With Multi-drug Resistant Mycobacterium Tuberculosis (MDR-TB).**

**What type of data are you looking for?:** Individual Participant-Level Data, which includes Full CSR and all supporting documentation

**Research Proposal**

**Project Title**

Safety and tolerability of conventional MDR-TB regimens

**Narrative Summary:**

Multidrug-resistant tuberculosis (MDR-TB), defined as tuberculosis with documented resistance against both isoniazid and rifampin, occurs in almost half a million new cases per year. Toxicity from conventional regimens to treat MDR-TB is nearly universal. This project will use data from the placebo control arms of three completed clinical trials of regimens for the treatment of MDR-TB to make safety and tolerability comparisons to regimens containing new and repurposed drugs for MDR-TB treatment. The three trials that will be used to construct this historical control are the pivotal bedaquiline (NCT00449644) and delamanid (NCT00685360) Phase 2B trials, and the delamanid Phase 3 trial (NCT01424670). Contributing historical control evidence against which to compare regimens containing newer drugs will inform clinical decision-making and help mitigate adverse events in MDR-TB treatment.

**Scientific Abstract:**

Background: Conventional multidrug-resistant tuberculosis (MDR-TB) treatment regimens contain at least five drugs, last up to two years, and until recently included daily injections for eight months. Consequently, treatment is poorly tolerated: common adverse effects include nausea, arthralgia, diarrhea, ototoxicity, nephrotoxicity, and hepatotoxicity. In the absence of safety reporting in most high-burden MDR-TB countries, the true frequency of toxicities is unknown to clinicians, patients, and regulatory authorities.

Objective: To construct a historical control of participants who received conventional (i.e., longer, 18-24 month) MDR-TB regimens that will be used as a comparator against which to examine the safety and tolerability of new and repurposed drugs for MDR-TB treatment.

Study Design: Frequency, type, time-to-event, severity, and relatedness of AEs during treatment, and adverse events (AEs) requiring treatment discontinuation will be reported. An important feature of these separate sources of data is that they use different standards for reporting AEs. This study will harmonize the disparate AE reporting standards into a single standard (e.g., a single severity grading scale) across the trials. This will permit building an historical control that can be used as a comparator in future analyses that will examine the safety and tolerability of new and repurposed drugs for MDR-TB treatment.

Participants: Patients randomized to the placebo arms of the pivotal bedaquiline (NCT00449644) and delamanid (NCT00685360) Phase 2B trials, and the delamanid Phase 3 trial (NCT01424670).

Main Outcome Measure(s): Primary outcomes are frequency, type, time-to-event, and severity of AEs during treatment of MDR-TB. Secondary outcomes are relatedness of AEs and AEs requiring
treatment discontinuation.

Statistical Analysis: Descriptive statistics will be used to compare, between exposed and unexposed groups, the proportion of severe AEs during the first 3 and 6 months of treatment. Time-to-event analyses will include plotting Kaplan-Meier survival curves by exposure group and testing the difference in hazards using the log-rank test. The following covariates will be considered as potential confounders in a multivariate Cox proportional hazards model that examines the effect of the exposure on the hazard of severe AEs: age, sex, weight, body mass index, HIV infection, receipt of antiretroviral therapy, other comorbidities, substance use, anti-TB drugs in regimen, and concomitant medications.

Brief Project Background and Statement of Project Significance:

MDR-TB is defined as tuberculosis (TB) with documented resistance against both isoniazid and rifampin. In 2021, there were an estimated 10.6 million new TB cases worldwide, with 450,000 new patients requiring treatment for MDR-TB [1]. Conventional MDR-TB treatment regimens contain at least five drugs, last up to two years, and include daily injections for eight months [2]. Toxicity from conventional regimens is nearly universal [3]. Consequently, treatment is poorly tolerated: common adverse effects include nausea, arthralgia, diarrhea, ototoxicity, nephrotoxicity, and hepatotoxicity [3]. In the absence of safety reporting in most high-burden MDR-TB countries, the true frequency of toxicities is spotty and unknown to clinicians, patients, and regulatory authorities. The complexity, length, and toxicity of conventional MDR-TB regimens limit access to treatment. Only 22% of new patients are treated, leading to ongoing preventable transmission and mortality.

Recent developments have made possible reduced length and complexity of MDR-TB treatment; toxicity implications—especially relative to the standard of care—remain uncertain. Three newer drugs, bedaquiline, pretomanid, and delamanid, and two repurposed drugs, clofazimine and linezolid, have been recommended by the WHO for MDR-TB treatment. The need to optimize the regimens for safety and tolerability is pressing. The main safety concern for these drugs is cardiotoxicity (bedaquiline, delamanid, and clofazimine). In pivotal Phase II trials, patients who received bedaquiline had a 14.0 millisecond (ms) mean increase in the corrected QT interval (QTc); this increase was 12.1 ms among patients who received delamanid [4, 5]. Significant QTc prolongation has also been reported when bedaquiline is co-administered with delamanid and clofazimine. QTc prolongation is a marker for increased risk of torsades de pointes, a life-threatening polymorphic ventricular tachyarrhythmia. Although no cardiac arrhythmias were reported in the bedaquiline trial, excess deaths (13%) in the bedaquiline group, compared with the placebo group (2%, P = 0.02), prompted a black box warning from the FDA [4].

This study is significant because it will permit larger and statistically more powerful comparisons of safety and tolerability of new and repurposed drugs, including the main safety concern of cardiotoxicity, for MDR-TB treatment than was previously available within each pivotal trial.

Specific Aims of the Project:

To examine the safety and tolerability of bedaquiline and delamanid within conventional MDR-TB regimens by comparing to a historical control of participants randomized to placebo arms of the pivotal bedaquiline (NCT00449644) and delamanid (NCT00685360) Phase 2B trials, and the delamanid Phase 3 trial (NCT01424670).

Study Design:

Methodological research

What is the purpose of the analysis being proposed? Please select all that apply.

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources
Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

The data sources for this analysis are the placebo arms of the pivotal bedaquiline (NCT00449644) and delamanid (NCT00685360) Phase 2B trials, and the delamanid Phase 3 trial (NCT01424670). The single inclusion criterion is that participants must have been allocated to the placebo arm in one of the three pivotal trials. The single exclusion criterion is that participants will be excluded from the analysis if they were randomized to a non-placebo arm.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The primary outcomes are frequency, type, time-to-event, and severity of AEs during treatment of MDR-TB. The secondary outcomes are relatedness of AEs and AEs requiring treatment discontinuation. Adverse event severity will be categorized with a harmonized severity grading scale that combines the disparate AE reporting standards into a single standard across the trials. The present YODA Project protocol will chiefly provide individual-level corrected QT interval (QTcF) data for participants allocated to the placebo arm in NCT00449644, which will be used to characterize QT prolongation AEs according to the outcome measures described above.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The main predictor/independent variable is receipt of TB treatment in a placebo arm of a pivotal trial, categorized by individual trial and in pooled historical controls (of 3 and 6 months of follow-up post-randomization). Other independent variables will be receipt of individual drugs, duration of receipt of individual drugs, and drug dose. For example, in the analysis of QT prolongation AEs, the primary and secondary outcomes described above will be characterized in each individual trial and in the pooled historical controls. In addition, QT prolongation will be characterized according to receipt, duration, and dose of individual QT-prolonging drugs in the treatment regimen among placebo arm participants (e.g., fluoroquinolones, clofazimine, others).

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Separate analyses will be performed based on treatment duration; both a three-month and a six-month historical control will be constructed.

Statistical Analysis Plan:

I will use descriptive statistics to compare, between exposed and unexposed groups, the proportion of severe AEs during the first 3 months, and subsequently first 6 months of treatment (the intended duration of bedaquiline and delamanid exposure in the exposed). Time-to-event analyses will include plotting Kaplan-Meier survival curves by exposure group and testing the difference in hazards using the log-rank test. In light of likely differences between the study populations, I will also evaluate the following covariates (available in all 3 datasets) as potential confounders: age, sex, weight, body mass index (BMI), HIV infection, receipt of antiretroviral therapy (ART), other comorbidities, substance use, anti-TB drugs in regimen, and concomitant medications. I will adjust for confounders (P < 0.10 in univariate models) in a multivariate Cox proportional hazards model that examines the effect of the exposure on the hazard of severe AEs.

Software Used:

RStudio

Project Timeline:
Anticipated project start date: October 2023
Anticipated analysis completion date: December 2023
Anticipated date manuscript drafted and first submitted for publication: January 2024
Anticipated date results reported back to the YODA Project: June 2024

**Dissemination Plan:**

Two target journals for publication are Clinical Infectious Diseases (CID) and The International Journal of Tuberculosis and Lung Disease (IJTLD). A target academic conference is the Union World Conference on Lung Health.

**Bibliography:**


**Supplementary Material:**