Background

The drug-resistant form of tuberculosis (TB) has the potential to reduce quality of life and increase the likelihood of mortality. Multidrug-resistant TB (MDR-TB) is treated with at least 6 months of injectable aminoglycoside (AG). Among MDR-TB patients, permanent hearing loss due to the ototoxic effects from long-term use of AGs is profound and may lead to early AG discontinuation. Despite the known risk of AG-induced hearing loss, selections and availability of less ototoxic antibiotics or monitoring of hearing loss are constrained because of limited public health resources in South Africa. It is known that excessive AG concentration, renal impairment, coinfection with HIV with a certain class of antiretroviral therapy (ART), severe systemic inflammation, malnutrition, preexisting hearing loss, and several demographic factors worsen a patient’s potential risk for AG-induced hearing loss during MDR-TB treatment. Among these risk factors, AG concentration needs to receive more attention because ototoxicity is dose-dependent. Maintaining therapeutic AG concentration aids in hearing loss prevention and cure of MDR-TB, but daily blood testing for drug concentration is impractical in South Africa due to financial constraints.

Project Aims

This study aimed to estimate the risk of AG-induced hearing loss among MDR-TB infected individuals in South Africa.

Specifically:
(1) To develop a prediction model of developing AG-induced hearing loss from MDR-TB treatment
(2) To explore the prognostic impact of cumulative AG exposure on AG-induced hearing loss in MDR-TB patients after injectable AG therapy initiation.

Theoretical Framework

The Adverse Outcome Pathway is a model often used to predict the pharmacokinetic and pharmacodynamic responses of a drug and the relationship of these to an adverse drug effect. The model consists of conceptual constructs and depicts existing knowledge of linkages between drug initiation, physiologic and molecular responses, followed by organ, then finally organism-level responses. Applying such an approach is helpful in hypothesizing relationships between different covariates when developing a prediction model associated with drug-induced adverse effect.

Methods, Procedures, and Sampling

Design and Setting
This prospective cohort study used a secondary analysis nested within an ongoing 5-year cluster randomized trial in South Africa. The parent study investigated the effects of nurse case management (NCM) in improving treatment outcomes in individuals with DR-TB. Data were collected across 10 public TB hospitals in the Eastern Cape and KwaZulu-Natal provinces.

**Participants**

The following patients were included: (1) all patients 13 years of age and older, (2) with microbiologically confirmed DR-TB using cartridge-based Xpert®, (3) those enrolled across 10 study sites, (4) those enrolled from November 2014 to June 2017, and (5) those who signed informed consent within seven days of treatment initiation. The following patients were excluded: (1) those receiving neither intramuscular kanamycin nor amikacin injection, and (2) those confirmed for drug-sensitive TB, XDR-TB, and pre-XDR—TB resistant to either fluoroquinolones or aminoglycosides—from baseline drug sensitivity tests that resulted during the first 6-months injectable phase of treatment.

**Predictors and Measures**

The following variables were abstracted from the parent study’s baseline data: (1) demographics and medical history including previous TB history, comorbidities, prescribed medications, and substance use; (2) presence of lung cavities on chest x-ray at DR-TB diagnosis; (3) serum creatinine levels to calculate estimated glomerular filtration rate (eGFR) for renal function; (4) HIV infection history including use of any ARTs and CD4 count; and (5) nutritional status measured by body mass index (BMI).

Since the parent study did not collect serum albumin levels, baseline albumin results were collected from the South African National Health Laboratory System (NHLS) online portal as a routine laboratory test for DR-TB treatment. Since no instrument exists for measuring poverty in South Africa, the conceptual definition of social deprivation² was used to select appropriate study variables to operationalize poverty in this study. South African social grants are given not only to the poor but also to the elderly, the disabled, or caregivers of a child with a disability.³ Thus, poverty was measured by a combination of social grant and employment status prior to MDR-TB diagnosis in the context of interdependency between TB and poverty in South Africa.⁴,⁵

The following variables were abstracted from the parent study’s baseline and monthly follow-up data during the injectable phase: (1) DR-TB treatment regimen including type of AG, AG dose, frequency, and adherence; (2) DR-TB confirmation test results including sputum culture and drug sensitivity tests; (3) auditory symptoms (i.e., hearing loss and tinnitus) and audiometric hearing evaluation results. Weekly measured regimen adherence and dosing information were used to calculate cumulative (or weekly) AG exposure per body weight (this study called standardized weekly AG exposure) =

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\frac{\text{prescribed daily AG dose (mg) x frequency of dosing over week (times per week)}}{\text{weight (kg)}}
\]

Hearing was tested monthly by audiometry to establish the lowest intensity of sound (= hearing threshold) in decibels (dB) that the person could hear at frequencies ranging from 250 to 8,000 Hz.⁶ Then, the level of hearing threshold was transferred to degree of hearing loss to define outcome of hearing loss.

This study defined pre-existing composite hearing loss as: (1) a hearing threshold outside of the normal range between -10 and 25dB in one or both ears at any frequencies in the range from 250 to 8,000 Hz, tested by either standard audio booth or computer-based portable audiometer (KUDUwave®) at baseline audiometry (aka pre-existing audiometric hearing loss); or (2) self-reported auditory symptoms including tinnitus or hearing loss at baseline. The outcomes of AG-induced hearing loss were further defined as: (1) clinically-identified hearing loss resulting in a change in treatment (i.e., reduced or stopped AG) due to ototoxicity confirmed by either
audiological or clinical evaluations; or (2) audiometric hearing loss defined as a worsened degree of hearing threshold compared to baseline hearing in the same range of frequencies in one or both ears.

Summary of Findings

Specific Aim 1
In this aim, we developed and validated a predictive model that can be used to calculate the probability of risk of hearing loss at clinical standard frequencies from 250 to 8,000Hz for the first 6 months of AG treatment among DR-TB patients. Although ototoxicity is dose-dependent, our model suggests that not only the initial dosage of AG regimen but also the baseline status of—malnutrition (i.e., underweight and hypoalbuminemia), immunosuppression (i.e., HIV coinfection with low CD4 count), advanced age, and pre-existing hearing loss—were highly impactful in predicting the incidence of hearing loss. This model demonstrated reasonable discrimination (AUC=0.715) and calibration ($\chi^2[8]=6.10$, $p=.636$). We also validated that the model in different clinical situations based on the availability of audiometric evaluation to expand this model becomes more practical and generalizable. The validation with the audiometric data in ultrahigh frequencies (i.e., $\geq$ 9,000Hz), in particular, found clinical potentials that this model may also be useful to predict early manifestations of AG ototoxicity (AUC=0.806; $\chi^2[8]=6.48$, $p=.593$). Such findings are practically meaningful because typical manifestations of cochleotoxicity begin with ultrahigh frequency hearing loss, which may not be clinically apparent, and are often undetected by standard audiology testing frequencies below 9,000Hz.\textsuperscript{2,3} In the clinical settings where audiometric evaluation is impossible, this model may be utilizable to discriminate those at higher risk in incompletion of the initial AG regimen due to ototoxicity without audiometry, which was validated in the clinically identified hearing loss cohort (AUC=0.599; $\chi^2[8]=4.34$, $p=.825$). This model represented a perfect positive predictive value (100%) at a cutoff of 85%. Thus, healthcare providers can triage patients whose predictive probability is higher than 85% to an AG-sparing regimen, enhancing the practicality of the model in clinical sites where an AG-sparing regimen is insufficient.

Specific Aim 2
This study found that the initial AG dosage is one of the key elements influencing the risk of AG-induced hearing loss and AG regimen modification during the DR-TB treatment intensive phase. We found that those who were exposed to AG more than 75mg/kg/week—the average dosage that the MDR-TB treatment guidelines suggested—were at higher risk of AG-induced audiometry-confirmed hearing loss, and that thereby the risk of AG regimen reduction or discontinuation is higher than those exposed to AG less than 75mg/kg/week (aHR=1.34, $p=0.38$). Since excessive AG concentration is a known risk factor for AG ototoxicity, standardized weekly AG exposure may also be considered a proxy surrogate measure of AG concentration in resource-limited settings where therapeutic drug monitoring is impractical. We expect that our findings may guide DR-TB providers to develop personalized interventions to prevent AG-induced hearing loss in medically underserved settings. Further, initial AG dosage was a matter of clinical judgement of regimen adjustment. In case where AG ototoxicity was detected either by audiological evaluation or by the presence of auditory symptoms of AG toxicity, DR-TB providers tended to stop the AG regimen if patients were receiving low dosage (< 3000mg/week), while they tended to reduce AG frequency rather than daily dose if patients were receiving medium or higher dosage (≥ 3000mg/week). Further studies are warranted to evaluate AG concentration between reducing frequency versus daily dose in this population to maximize therapeutic efficacy and minimize adverse effects.

Other risk factors of hearing loss, such as advanced age and pre-existing hearing loss, were also significantly associated with the hazard of audiometry-confirmed hearing loss and the
decision of AG regimen modification. This finding weighted not only practical but also policy-level concerns because, a high prevalence of pre-existing hearing loss and potential presbycusis was found in this study population. These findings highlight the importance of not only baseline screening of hearing as a routine practice, but also more frequently repeated audiometric hearing monitoring. Also, offering a less ototoxic regimen for elderly patients with pre-existing hearing loss should be considered to avoid severe hearing loss.

**Recommendations**

South Africa has made tremendous strides in improving DR-TB treatment including introduction of new regimens such as 9-month short-course regimens or injection-sparing regimens. The developed AG-induced hearing loss prediction model may be useful to allocate AG-sparing regimens cost-effectively in clinical sites where an AG-sparing regimen is insufficient. Predictors in the model were selected from existing clinical data collected based upon South African national guidelines, so there is no need to conduct additional lab tests or clinical evaluations to use the developed model. Since this model represented 100% positive predictive value at a cutoff of 85%, healthcare providers can prioritize patients whose predictive probability is higher than 85% to an AG-sparing regimen. Although we expect that predicting hearing loss risk will reduce ototoxic drug use for those at highest risk and will thereby reduce hearing loss, other physio-psychological and socioeconomic factors would influence the outcome of hearing loss since each individual is unique.

**Financial Summary**

See attachment from Johns Hopkins University

**Testimonial**

This research would not have been possible without the assistance of the STTI Global Nursing Research Grant. The grant allowed me to make regular site visits for data collection and data quality assurance/control procedures. In addition, I was able to purchase necessary supplies to support the operations of conducting the study. For PhD students, funding opportunities are limited and so support from the STTI was enormously helpful to complete my doctoral degree with a rigorous training experience. Thank you!
References


