**Study Protocol**

**Prospective Study of Drug Resistant Tuberculosis and HIV Infection Treatment Outcomes in KwaZulu-Natal, South Africa   Version 1.3**

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**Specific Aims**

**Specific aim 1:** To determine clinical outcomes and predictors of treatment success and failure among DRUG RESISTANT TB patients, for patients initiated on drug resistant tuberculosis treatment at King George V Hospital, KwaZulu-Natal, South Africa.

**Hypothesis 1a:** Among HIV co-infected DRUG RESISTANT TB patients: patients with CD4 T cell counts less than 200 cells/ ml compared to HIV co-infected XDR-TB patients with higher CD4 T-cell counts.

**Hypothesis 1b:** DRUG RESISTANT TB patients with resistance to more second line injectable anti-tuberculosis agents will have worse outcomes compared to DRUG RESISTANT TB patients without such resistance.

**Hypothesis 1c:** DRUG RESISTANT TB Patients able to tolerate intramuscular injectable agents for greater than 12 months will have better treatment outcomes compared to patients treated for shorter time periods.

**Hypothesis 1d:** HIV co-infected DRUG RESISTANT TB patients on anti-retroviral medications regardless of CD4 T cell count will have better treatment outcomes compared to HIV co-infected DRUG RESISTANT TB patients not on antiretroviral medications.

**Specific aim 2:** To determine incidence, type and severity of adverse drug reactions among DRUG RESISTANT TB patients on second-line TB drugs.

**Hypothesis 2a:** Patients with severe adverse drug reactions will be at increased risk for treatment failure and death.

**Hypothesis 2b:** Patients co-infected with HIV and taking HAART will be at increased risk for adverse drug reactions compared with HIV co-infected patients not on HAART, and with DRUG RESISTANT TB patients who are not HIV infected.

**Background**

*Mycobacterium tuberculosis* (*M. tuberculosis*) is a leading cause of mortality world-wide with 1.7 million deaths reported due to tuberculosis disease (TB) in 2006. Although the global incidence of tuberculosis has stabilized over the past five years, TB causes disproportionate disease and mortality in Africa, largely attributable to TB/HIV co-infection (TB/HIV). Multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) largely attributed to a failure of public health systems, are increasingly identified as one of the greatest challenges to TB control efforts in Africa and world-wide. The phenomena of drug-resistant TB with HIV co-infection, first described in an outbreak in South Africa, threaten to overwhelm fragile health systems.

In 2006, there were greater than 90,000 tuberculosis (TB) cases diagnosed in the province of KwaZulu-Natal (KZN), South Africa resulting in an incidence rate of 970 per 100,000 persons. This high incidence of TB is coupled with an explosive HIV epidemic. It is estimated that 70% of TB patients in KZN are HIV seropositive and greater than 85% of the excess cases of TB are attributable to the HIV/AIDS epidemic. Resistance to TB drugs is not a new public health problem. However, it is regions like Southern Africa, with high HIV prevalence rates, that are cause for the greatest concern.

 The most resistant form of TB, XDR-TB is defined as resistance to isoniazid, rifamycin, fluoroquinolones and one of three injectable second-line anti-TB agents: capreomycin, kanamycin, and amikacin. XDR-TB cases are being increasingly reported world-wide and comprise a rising percentage of all drug resistant TB cases.

**Rationale**

King George V Hospital (KGV) is a 320 bed public sector specialist referral TB hospital in Sydenham, KZN. It is the only central referral hospital for all MDR and XDR-TB cases in the province. The hospital has specialized treatment facilities for drug resistant TB patients. There are 180 beds allocated for TB; of these 30 are for spinal TB and 30 are for surgical thoracic TB. KGV has on-site laboratory and radiology facilities as well as a

pharmacy which provides medications for inpatients and outpatients. All culture and DST are performed at a central provincial laboratory (Albert Luthuli Hospital Microbiologic Lab). Patients with drug resistant and acute TB disease are admitted to the hospital where they undergo appropriate diagnostic procedures, are initiated on treatment and monitored as inpatients for variable periods of time, and then returned to their community of origin with monthly follow up appointments at KGV.

In 2007, over 1100 MDR-TB patients and 162 XDR-TB patients were admitted to King George Hospital. Currently, almost all inpatients at KGV have MDR-TB or XDR-TB. Occupancy is currently at 100% with approximately 50 patients on a waiting list for admission. Prior to December 2006 second line TB drugs were poorly available in KZN and therefore XDR-TB patients were not being treated with adequate regimens of active anti-TB drugs. As of July 2008 XDR-TB patients at KGV are being initiated on Capreomycin, Para amino salicylic acid (PAS) in combination with other TB treatment agents.

Among HIV uninfected patients in developed countries, XDR-TB is difficult to treat and has worse treatment outcomes than MDR-TB. Preliminary data from a prospective trial of drug-susceptible TB and HIV in KwaZulu-Natal has shown improved outcomes with early anti-retroviral therapy. Whether this preliminary result in drug-susceptible TB will hold true for drug-resistant tuberculosis is not known.

Treatment outcomes of XDR-TB among HIV co-infected patients in developing countries have not been reported. This study will represent the first prospective treatment outcomes data among XDR-TB patients in Africa, the majority of whom are HIV/TB co-infected.

**Methods:**
Eligible patients will include all patients admitted to KGV from March 1, 2009 through February 28, 2009 with drug susceptibility testing consistent with DRUG RESISTANT TB. Written informed consent will be obtained from each patient in either English or isiZulu by trained study staff. Informed consent will be obtained from the parent or

guardian for patients younger than age 18. Patients unable to give informed consent will not be considered eligible.

It is estimated that we will need to recruit 68 patients during the study period in order to have an adequate sample size. Sample size was calculated based on **Hypothesis 1a** (see specific aims above) using an alpha level of 0.05%, an 80% power to detect a difference between groups. Estimates of frequency of CD4 counts and mortality differences between the groups were obtained from preliminary retrospective data. Sample size calculation was performed using statistical software (Epi Info 3.5.1, CDC, Atlanta, Georgia, USA).

Using standardized data collection tools (Form A and Form B appended to this protocol) we propose to perform a systematic review of demographic, clinical and treatment characteristics, HIV co-infection and outcome of both TB and HIV. Data to be collected includes: demographics, previous source of care, clinical features, laboratory parameters, therapeutic interventions, adverse drug reactions (appendix 1), surgical interventions, clinical progress, and standard TB and HIV outcomes. All standard laboratory and clinical tests including chest radiographs, HIV test results, viral loads, and CD4 counts will also be captured on each patient.

Patients will be discharged from KGV at the discretion of the medical staff. On discharge from KGV, study staff will follow up with the participants on a monthly basis and collect clinical, behavioral, and other treatment outcomes.

**Molecular Epidemiology**

We will collaborate with the Medical Microbiology laboratory group at the University of KwaZulu-Natal (UKZN) led by Professor Wim Sturm to perform assays to characterize the molecular epidemiology of isolates. All patients who enroll in the study will have a sputum isolate collected within 2 weeks of initiation on therapy. M. tuberculosis (MTB) patient isolates that are viable will be examined with IS6110 restriction-fragment–length polymorphism (RFLP) analysis using standardized methods. All MTB patient isolates will be examined using

spoligotyping ('spacer oligotyping'). All MTB isolates will be examined using 24 loci mycobacterial interspersed repetitive units (MIRU-24) or 15 loci mycobacterial interspersed repetitive units (MIRU-24) depending on the preference of the UKZN laboratory group.

**Breath Testing**

Exhaled breath (EB) collection has no apparent risk. The EB technique has been r the last decade in a variety of research and clinical settings to detect carcinoma without any reported adverse outcomes. Patients with drug resistant tuberculosis tend to be ill and unable to produce adequate volumes of good quality sputum which is necessary to diagnose TB, thus we would like to collect breath moisture (which will be easy to collect from ill patients) and determine if we are able to extract *M tuberculosis* DNA and amplify it for use in standard diagnostic techniques. These specimens will be shipped to the TB laboratory at Albert Einstein College of Medicine , Bronx, NY. If this technique is successful, then the investigators undertake to build local capacity in the use of this technique.

**Patient Privacy and Confidentiality:**

Patient informed consent will be obtained from each study participant. Permission from the necessary hospital authority will be obtained for accessing patient medical and demographic records. Permission from the KwaZulu-Natal Department of Health will be obtained for the study. No patient names or hospital ID numbers will appear on study data analysis forms. Patients will be represented on study data sheets with study numbers. The key to patient study ID numbers and patient names and hospital numbers will be kept in a secure location as hard copies by the principal investigator.

**Expected Outcomes of DRUG RESISTANT TB patients on Therapy:**

      Demographic, Clinical, Behavioral, and Social Characteristics

      Sputum conversion rates, and time to conversion

      Mortality rate, Case-Fatality rate

Cause of death

HIV prevalence, Initial CD4 counts and opportunistic infections

Viral load and CD4 trends on anti-TB therapy

Type and prevalence of Adverse Drug Reactions (see Appendix 1)

TB Resistance patterns

Anti-TB drug regimens; initial as well as medication changes

Duration of Anti-TB therapy

Co-Morbid conditions

Statistical analysis will be conducted using the SAS (version 9.1.; SAS Institute Inc., Cary, NC, USA) software.

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APPENDIX 1.

## TABLE . DEFINITIONS OF ADVERSE DRUG REACTIONS (ADRS)

| EVENT | DEFINITION |
|---|---|
| Nausea, vomiting, anorexia, diarrhea | As documented in patients chart by treating physician, not ascribed to other condition |
| Drug-induced liver injury (DILI) | ALT elevation more than three times the upper limit of normal (ULN) in the presence of hepatitis symptoms and/or jaundice, or five times the ULN in the absence of symptoms. |
| Nephrotoxicity | Elevation of at least two sequential creatinine values >141 mmol/l* |
| Hypokalemia | One or more documented serum potassium values of <2.5 mEq/l (severe), or <3.0 mEq/l (moderate)* |
| Hypomagnesemia | One or more documented serum magnesium values of < 1.5 mEq/l* |
| Hypothyroidism | TSH documented >10 IU/ml on one or more occasion in a patient without known preexisting or symptoms consistent with preexisting hypothyroidism |
| Depression | Clinical criteria per treating physician, based upon DSM-IV |
| Psychosis | Clinical criteria per treating physician, based upon DSM-IV |
| Seizure | Event consistent with seizure documented in the medical record (tonic-clonic movements, sudden loss of bowel/bladder function, post-ictal confusion) |
| Ototoxicity | Significant hearing loss as documented by audiometry or physical exam, or new positive Romberg test on physical examination |
| Drug rash | Any dermatologic reaction felt by treating physicians to be related to anti-TB medications |
| Neurotoxicity | New weakness, pain, paresthesias, or numbness in the distal extremities as diagnosed by physical examination |
| Hypersensitivity Reaction | New fever, joint pain, and rash in association with drug administration |