PROTOCOL

Promoting Engagement in the Drug Resistant TB-HIV Care Continuum in South Africa

PRAXIS Study (**PR**ospective study of **A**dherence in M/**X**DR-TB **I**mplementation **S**cience)

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Sponsored by

Study Team

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Acronyms

ART	Antiretroviral Therapy
AIDS	Acquired Immunodeficiency Syndrome
BREC	Biomedical Ethics Research Council
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CDC	Centers for Disease Control and Prevention (United States)
CD4	CD4 lymphocyte or helper T cell (a type of white blood cell)
FGD	Focus Group Discussion
GCP	Good Clinical Practice
HC	Health center
HCW	Health care worker
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Offices
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
KDH	King DinuZulu Hospital Complex
KZN	KwaZulu-Natal
M/XDR-TB	Multi-drug resistant tuberculosis or Extensively drug resistant tuberculosis
MDR-TB	Multi-drug resistant tuberculosis
MTB	*Mycobacterium tuberculosis*
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NTP	South African National TB Program
PE	Peer educator
PEPFAR	President's Emergency Plan for AIDS Relief
PLWH	People Living with HIV
PID	Patient Identifier
RA	Research Assistant
sIMB	situated-Information Motivation Behavioral Skills Model
SOC	Standard of Care
SOP	Standard Operating Procedures
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	United States Agency for International Development
VAS	Visual Analog Scale
WHO	World Health Organization
XDR-TB	Extensively drug resistant tuberculosis

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1   STUDY OVERVIEW

Promoting Engagement in the Drug Resistant TB-HIV Care Continuum in South Africa

1.1   Summary

The goal of this study is to understand adherence and retention in care for multi-and extensively drug-resistant tuberculosis (M/XDR-TB) patients using a mixed methods approach.

1.2   Background

Tuberculosis (TB) remains the leading cause of morbidity and mortality worldwide among people living with HIV (1). Globally, the incidence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB), the most drug-resistant forms of TB, has approximately doubled over the past fifteen years (1-3). Nowhere has this increased incidence generated more concern than in South Africa where interactions between TB and generalized HIV epidemics are causing 'explosive' TB incidence (4-6) and case-fatality are threatening to undermine the progress reached with antiretroviral therapy (ART) (7, 8).

Medication adherence, a key predictor of outcomes in M/XDR-TB and HIV treatment, is understudied in high burden TB-HIV settings (9-11). Patient losses during transitions in the care continuum are frequent (12), increase mortality and limit control of the linked epidemics. Demands of M/XDR-TB HIV treatment are severe including extraordinary pill burden, severe adverse effects, lengthy treatment, isolation and stigma with few parallels in modern medicine (13-15).

1.3   Specific Aims

Specific Aim: To characterize medication adherence and retention in care in the drug-resistant TB-HIV care continuum

Hypothesis A. M/XDR-TB HIV patients will be more adherent to ART than to TB medications and differential adherence will be predicted by socio-medical risk factors. (N=200)

Hypothesis B. Barriers and facilitators to medication adherence and retention in care for M/XDR-TB HIV patients identified through in-depth interviews and focus group discussions with patients and health care workers will cluster into informational, motivational, skills-based and social-structural factors.

1.4   Methods

This is a prospective observational cohort study for patients newly diagnosed with M/XDR-TB and HIV initiating treatment. A mixed methods approach will be employed to address the complex research questions of distilling determinants of barriers and facilitators to both TB medications and ART; this study will employ complementary qualitative and quantitative methodologies for assessing differential adherence to TB medications and ART.

A sub-set of patients and health care workers (HCW) will be approached for participation in focus group discussions.

1.5   Population

Adult patients with newly diagnosed active pulmonary M/XDR-TB (≥ 18 years old), confirmed by MTB culture results, admitted for routine care at King DinuZulu Hospital in Durban, South Africa will be approached for enrollment. Only patients with capacity for consent will be included in the study. See Inclusion and Exclusion criteria below for further details.

Healthcare workers will be approached for participation in focus group discussions.

1.6   Study Duration

Approximately two years will be allowed for enrolment. Patients will be followed until the end of treatment (approximately 4 years total).

1.7   Participant Duration

All participants will be followed monthly for 6 months from enrolment, every 6 monthly thereafter, through the end of treatment (18 to 24 months after treatment initiation for M/XDR-TB). See Schedule of Evaluations for further details.

1.8   Potential Significance

The study findings may be used to inform programmatic management and the development of interventions for promoting adherence for M/XDR-TB HIV patients with an overarching goal of promoting patient engagement in a care continuum.

Ultimately, the mixed methodology developed during this study may be used to evaluate the effectiveness and acceptability of an intervention in improving clinical outcomes and reducing patient barriers to adherence and retention in care (20).

2   PERSONNEL AND TRAINING

2.1   Roles

<u>Roles of Lead Investigators</u>: Investigators will provide leadership and mentorship, supervise the study team and monitor the project, develop the study protocol. Drs. Padayatchi and O'Donnell are the co-Principal Investigators of this study.

Dr. O'Donnell with Dr. Padayatchi will be responsible for the overall conduct of the study and will supervise all study related activity.

2.2   Staff Training

All study staff will have current good clinical practice (GCP) training. The study timeline will include 6 months for training study staff. Training in study protocols will be performed prior to recruitment of patients and refresher training will be performed regularly. Supervision will be provided to ensure participant safety and good study conduct.

3   BACKGROUND AND SIGNIFICANCE

3.1   Drug resistant tuberculosis remains prevalent in South Africa

The emergence of drug-resistant strains of Mycobacterium tuberculosis (MTB) presents a significant threat to global TB control efforts and international health (21). This includes multidrug resistant TB (MDR-TB) defined as TB resistant to isoniazid and rifampicin, the most effective first-line antimycobacterial agents; and extensively drug resistant TB (XDR-TB) the most drug-resistant form of TB (22). In 2012, it is estimated there were 450,000 incident cases of MDR-TB (23), an increase of 80% from estimates in 2000 (24). Global MDR-TB prevalence is estimated to be 1-1.5 million (23). South Africa has approximately 18% of the global burden of laboratory-confirmed MDR-TB and the highest number of confirmed XDR-TB cases (23, 25).

In KwaZulu-Natal province, South Africa, admissions for MDR-TB have increased 400% over the past 6 years and admissions for XDR-TB have increased from fewer than 10 to 162 admissions per year (26). King DinuZulu Hospital Centre where this study will be sited initiates on treatment approximately 1500 patients with either MDR-TB or XDR-TB per year. The increase in TB in South Africa is attributed to endemic HIV/AIDS (4). Eighty-three percent (83%) of TB patients with known status are HIV co-infected (27). Our team has reported on treatment outcomes in XDR-TB and HIV patients, with low rates of culture conversion, emergent drug resistance on treatment, and high mortality in XDR-TB patients not on antiretroviral therapy (ART) at treatment initiation (26, 28) (**Figure 1**).
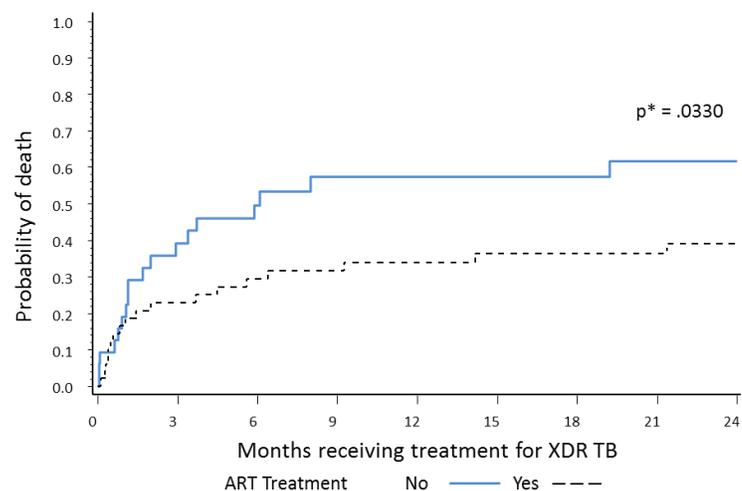

Figure 1. Kaplan Meier survival of XDR-TB HIV patients stratified by antiretroviral therapy (ART) through 24 months of treatment (N=82)

3.2   Suboptimal adherence to medication is linked to drug resistance and poor outcomes

Medication adherence, a key predictor of outcomes in multi-and extensively drug-resistant tuberculosis (M/XDR-TB) and HIV treatment, is understudied in high burden TB-HIV settings (9-11). Patient losses during transitions in the care continuum are frequent (12), increase mortality and limit control of the linked epidemics. Demands of M/XDR-TB HIV treatment are severe including extraordinary pill burden, severe adverse effects, lengthy treatment, isolation and stigma with few parallels in modern medicine (13-15).

Research by our team shows adherence to TB medications (67.7% adherent) is significantly lower (p < 0.001) than adherence to ART (88.2% adherent) in XDR-TB HIV patients on treatment in KwaZulu-Natal, South Africa (29, 30). Survival without M/XDR-TB cure may increase community drug-resistant TB transmission (13, 31), and lead to loss of the first new TB drugs in a generation through acquired drug-resistance (32-34). Conversely if we are able to support M/XDR-TB HIV patients to achieve the same level of adherence to second-line TB medications as they do with ART (35), we may dramatically improve survival, interrupt transmission of resistant TB strains (36, 37), and protect vital new drugs (13, 32).

To have high impact in improving adherence and outcomes in KwaZulu-Natal, South Africa (35, 38, 39), we must first understand the clinical, social and structural determinants (15, 20, 40-44) of adherence to second-line TB medications and ART comprehensively (15, 45).

3.3 TB treatment adherence

We will employ a mixed-methods approach (46-50) to address the complex research questions of distilling determinants (48, 51-55). This approach is well-suited to M/XDR-TB HIV adherence research in South Africa where clinical, socio-behavioral, and structural factors likely exert considerable influence on adherence. Our team includes international experts in implementation science, behavioral science, medication adherence, qualitative methods, and treatment outcomes in drug-resistant TB and HIV.

3.3.1 Quantitative approach to retention in care and adherence in treatment of drug-resistant TB-HIV

Medication adherence is critical for both HIV and TB outcomes, and suboptimal adherence mediates the development of antimycobacterial and antiretroviral drug resistance on treatment (10, 56, 57). Early studies have shown that approximately 95% adherence to ART is needed to ensure HIV viral suppression (37, 58). Later studies using more potent and durable regimens have demonstrated viral suppression with lower adherence (59, 60). Clinical trials of drug-susceptible TB treatment have shown that 95% of patients are capable of successful outcome with direct observation and support by study personnel (61). However, under operational conditions many patients are not retained in treatment or default their TB treatment; successful outcomes range from 55-95% (62, 63).

Patient adherence in HIV and TB treatment have been recently reviewed (64, 65). A 'gold-standard' for measuring medication adherence in either field is controversial and each method has strengths and weaknesses (66). Low adherence to second-line TB medications is not surprising. Patients with M/XDR-TB take on average 8 antimycobacterial medications (in addition to ART) with numerous significant adverse effects including nausea, skin discoloration, neuropsychiatric effects, renal toxicity, ocular and ototoxicity (28, 67). In retrospective studies, between 41 and 58% of M/XDR-TB patients experience serious side effects (28, 68). These regimens need to be taken for greater than 18 months (MDR-TB) and greater than 24 months (XDR-TB) with a low probability of successful outcome particularly in resource poor settings (1, 28, 69). Better regimens for drug-resistant TB are therefore urgently needed. For the first time with the regulatory approval of medications such as bedaquiline, delaminid, and linezolid, such improved drug-resistant TB regimens are on the horizon (70, 71). The new MDR-TB drugs will be part of prolonged multidrug regimens; medication adherence will remain a critical determinant of effectiveness and durability.

In this study, quantitative adherence will be measured using several complementary methods. These include thirty day and seven day recall (72), visual analogue scales (73-75), and pill count using medication an electronic monitoring system (such as Wisepill technologies that quantifies medication doses taken by study participants (76, 77).

3.3.2 Qualitative approach to characterize determinants of adherence in drug-resistant TB-HIV

Adherence to both TB medications and ART may be affected by patient's knowledge, attitudes, and beliefs (78, 79). These are often inextricable from poverty, gender, education, stigma, and other social, structural, and cultural factors (14, 64, 80-82). In comparative work with patients receiving treatment for either HIV or drug-susceptible TB, TB patients have reported lower scores related to

quality of life, social belonging, support, and symptom control compared to those on ART (83). In co-infected TB-HIV patients, dual non-adherence has been associated with poverty, tobacco use, and other co-morbidities (80). Qualitative research, through its focus on experience-based narratives and socio-structural factors, is able to form hypotheses about individual behaviors and contextual factors that can inform programmatic development as well as future research (45, 84-87). Qualitative work has contributed deeper understanding of the processes by which TB and HIV stigmas, nondisclosure, and lack of support interact with economic and health system constraints, to impede patients' capacity to adhere to treatment (14, 15, 35, 64). The ways in which these personal and social factors intersect and influence patients' decision-making for HIV and drug-resistant TB is unknown. There is a need to engage with these multidimensional concepts using qualitative methods to understand the individual, community, familial, and health system level determinants of adherence from the perspective of co-infected patients.

4 STUDY OBJECTIVES AND AIM
4.1 Rationale

Improved treatment of drug-resistant tuberculosis and HIV has been identified as a research priority (88). Implementation of the project will increase local scientific capacity to conduct implementation research by 1) developing programmatic links between central hospitals and de-centralized, community-based treatment programs for drug-resistant TB-HIV, 2) building on existing President's Emergency Plan for AIDS Relief (PEPFAR) program strengths using the Centre for the AIDS Programme of Research in South Africa's (CAPRISA) excellent research infrastructure to generate evidence-based recommendations, 3) training and developing junior researchers in implementation science and mixed methods approaches (89).

Successful completion of the Aim will substantially advance our understanding of M/XDR-TB HIV adherence dynamics and develop an important set of innovative clinical tools for the assessment and support of dual TB and ART adherence. Specifically, we will develop a model for clinical assessment and prediction of second-line TB medication and ART adherence and delineate the effect of the addition of ART on overall adherence in M/XDR-TB HIV co-infected patients (*Hypothesis A*). Importantly we will qualitatively explore patients' perspectives on adherence (*Hypothesis B*) to give insight into the complex narratives within which patients make decisions.

4.2 Specific Aim and Hypotheses

Specific Aim. To characterize medication adherence and retention in care in the drug-resistant TB-HIV care continuum

Hypothesis A. M/XDR-TB HIV patients will be more adherent to ART than to TB medications and differential adherence will be predicted by sociomedical risk factors. (N=200)

Hypothesis B. Barriers and facilitators to medication adherence and retention in care for M/XDR-TB HIV patients identified through in-depth interviews and focus group discussions with patients and health care workers will cluster into informational, motivational, skills-based and social-structural factors. (N=80)

5   METHODS
5.1   Overview

<u>Time line</u>
Dates are approximate
- 6 months for staff training
- Approximately 24 months for enrolment (200 patients)
- Participants will be followed monthly through 6 months and then 6-monthly until the end of treatment
- Plus end of treatment visit

<u>Overview of Study Processes</u> (see 6.1   Schedule of Study Evaluations)
- Informed consent
- Baseline (Intake) Assessment
- Medical history, etc.
- At monthly visits measure medication adherence to ART and second-line TB medications questionnaires about sociomedical determinants of adherence.
- Focus group discussions will start approximately 2-6 weeks after start of study enrolment

5.2   Study Design
This is a prospective observational cohort study utilizing a mixed methods approach.

5.3   Population and Study Setting
These studies will be conducted within the established implementation science research infrastructure at the CAPRISA Treatment Clinical Research Site in Durban, South Africa which has a track-record of performing high quality, impactful implementation science studies (90, 91).

5.4   Recruitment
This is a prospective observational cohort study for people with HIV that have been diagnosed with

M/XDR-TB and are initiating treatment at King DinuZulu Hospital (KDH), a centralized TB referral hospital in Durban, South Africa where M/XDR-TB patients beginning treatment are referred for treatment. Consecutive patients meeting inclusion criteria will be approached at KDH for enrolment into the study by a member of the study staff. Patients willing to participate will complete an Informed Consent form.

5.4.1   <u>Inclusion Criteria</u>
1) Age ≥ 18 years
2) MTB culture positive with at least isoniazid and rifampicin resistance **OR**
Molecular drug susceptibility test confirming resistance to at least isoniazid and rifampicin **OR**
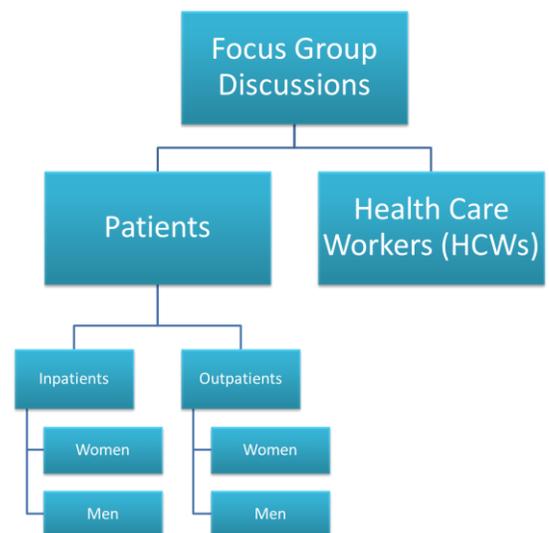Polymerase chain reaction test (Xpert MTB/RIF) result showing MTB positive and

Figure 2. Focus group discussions will comprise patients and health care workers stratified by gender and inpatient versus

RIF resistance. Patients enrolled with only a Xpert MTB/RIF result will be withdrawn if their subsequent susceptibility test or molecular drug susceptibility test reveals rifampicin monoresistance.

3) Initiating treatment for M/XDR-TB which includes at least 2 new medications
4) Have capacity for informed consent
5) HIV Positive Patients: on ART or initiating ART within the following 4 weeks as per clinician recommendation

5.4.2   Exclusion Criteria
Pregnancy
Prisoners
Discretion of IOR or clinician

5.5   Focus group sub-study

5.5.1   Main study sub-cohort

A sub-cohort of study participants from main study will be approached for participation in FGD.

We anticipate that there will be 4 'stages' of FGDs – inpatient (1), post discharge (2), late outpatient (3), and ambulatory (4, never hospitalized). We will hold 4 patient FGDs each in stages 1, 2 and 3, and 2 FGDs in stage 4 (total 14 patient FGDs). Each patient FGD will have 3-8 unique patient participants. (The overall target FGD patient sample is 60, but may range between 42 and 112 depending on the actual number of participants who present at the time of the FGD.) Individual interviews will be arranged where FGDs are not feasible. The timing of and classification of stages may evolve as data is collected.

Participants must be fluent in either English or isiZulu. A purposive sample based on age, gender, duration on treatment, and treatment site (in/outpatients) will be sought to capture diverse viewpoints (**Figure 2**). Inpatients will be asked to participate in three FDG throughout the course of treatment. Ambulatory participants will participate only in stage 4.

Timing of FGDs:

1) Inpatient (2-6 weeks following the initiation of treatment)
2) Post discharge (<2 months following discharge)
3) Late Outpatient (>2 months following discharge)
4) Ambulatory (2-6 weeks post treatment initiation)

5.5.2   Healthcare workers

We will hold approximately 6 HCW FGDs in the first year of the study. Each HCW FGD will have 3-6 unique HCWs. (The overall target HCW sample is 20, but may range between 12 and 36 depending on the actual number of participants that present at the time of the FGD.) Individual interviews will be arranged where FGDs are not feasible.

Healthcare workers meeting the following criteria will be approached for participation in the focus group discussions: (i) Employed at study site King DinuZulu Hospital for >6 months; (ii) Engaged in delivery of clinical and/or social services; (iii) Capacity for informed consent.

6   DATA COLLECTION

6.1   Schedule of Study Evaluations

Procedures	Baseline (enrolment)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every 6 months	End of Treatment
Informed consent[+]	x								
Baseline (Intake) Assessment	x								
Complete medical history chart abstraction	x								
Sputum Sample collection for storage	x	x	x	x	x	x	x		x
Hair Sample collection for storage[€]			x		x		x		
Blood Sample collection for storage	x		x				x		x
Monthly Follow-up questionnaires[ʊ]		x	x	x	x	x	x		
sIMB questionnaire[α]		x		x			x		
7-day recall for ART and TB Medication		x	x	x	x	x	x		x
30-day recall for ART and TB Medication		x	x	x	x	x	x		x
Visual analog scale for ART and TB	x	x	x	x	x	x	x		x

Medication Adherence[□]									
Pill count by Wisepill electronic pillbox		x	x	x	x	x	x		
End of Study questionnaire									x
Focus Group Discussions[φ]		x*					x**	x***	

[+]Separate informed consent will be obtained for HCW prior to participating in FGD
[€]We anticipate taking hair samples from all participants at least twice and/or from a subset of all participants, timing will vary
[ᴑ]Follow-up questionnaire may be completed over phone if necessary
[α]We anticipate administering the sIMB questionnaire to all participants at least twice and/or to a subset (timing will vary)
[□]If follow-up visit is completed by phone, Visual Analogue Scale Assessment will be omitted
[φ]Fourth type of focus group will be conducted with ambulatory participants (never hospitalized)
*First focus group will be conducted between 2-6 weeks following enrollment (see Section 4.5 for additional detail)
**Second focus group will be done within 2 months following discharge from hospital
***Third focus group will occur more than 2 months following discharge from hospital

6.2   Study Visit Schedule

Main cohort

Study participants will complete study assessments at baseline (enrollment) and monthly for the first six months. Ideally follow-up questionnaires will be completed in person but allowance will be made for telephonic completion of questionnaires. Additional questionnaires will be completed following discharge (community treatment follow-up) and at the end of treatment. See section 6.1 for additional details.

Focus Group sub-Cohort

Patients will be approached to participate in focus group discussions after completing ≥2 weeks of treatment. See section 5.5 for additional details.

Reimbursement

Participants will be reimbursed for time, travel and inconvenience for each study visit, and for participating in focus group discussions.

6.3   Clinical Data Elements

Data for the study will be collected at the following visits: a) baseline (enrolment) visits, b) monthly clinical visits, c) follow-up or end of treatment visits, and d) at focus group discussions. See Appendix for all questionnaires. Questionnaires will be administered by study staff fluent in both English and isiZulu.

A standardized data collection instrument will be used in this study.

Clinical Study visits

Baseline (enrolment) visits: Data will be abstracted from patient charts and medical history. Study staff will administer baseline (intake) assessment collecting sociodemographic characteristics, medical history, knowledge, attitudes and beliefs. These data will include date of TB treatment initiation, date of ART initiation, information regarding past history of TB, smear and culture results.

Participant Contact Information: At the time of study enrolment, participants will disclose their names, addresses and phone numbers so that they may be contacted by the study staff regarding study visits. Sensitive data will be kept separately from study materials and will not contain patient study identifiers. This will be updated at monthly visits.

Monthly clinical visits: Study staff will collect sociodemographic, and microbiologic data at each scheduled visit including self-reported adherence, including VAS, 7-day recall, and 30-day recall. Additionally, the situated-Information Motivation Behavioral Skills (sIMB) questionnaire will be administered at varied time points before and after hospital discharge and in never hospitalized participants. Timing will be varied to capture diverse viewpoints throughout treatment.

Electronic Data: Participants will be provided with electronic pillboxes at baseline (enrolment). Electronic data regarding adherence will be collected monthly until Month 6.

End-of-treatment Interview: When participants complete treatment, he or she will complete an interviewer-administered standardized questionnaire to collect data including knowledge, attitudes, adherence, treatment acceptability, beliefs and outcome.

Focus Group Discussions

FGD will be audio recorded, and recordings will be transcribed verbatim, checked for accuracy, translated, anonymized, and entered into NVivo® database or other qualitative data software to facilitate coding and constant comparative analyses across the data set (92, 93).

6.4 Biological Specimen Collection, Preparation, Handling and Shipping
6.4.1 Biological Specimen collection

In addition to a medical chart review, participants will have specimens collected.

At the baseline (enrolment) visit, specimen collection may include:

- 10 ml blood
- Two sputum samples

At follow-up visits, additional specimen collection may include:

- 10 ml blood
- Two sputum samples
- fibers of hair (approximately 200 hairs) from the occipital region of the scalp

The biological specimens will be stored for future studies of transcriptomic and immune biomarkers of TB treatment response.

The specimens will be coded with the patient identifying number, and stored separately from any personal or sensitive information or link to the consent form. The investigators will receive only the coded specimens.

Participants will be followed-up for additional specimen collection:
See Section 6.1.

6.4.2 Laboratory Evaluations

Blood
-Biobanking for future studies

Sputum
Sputum tests may include but are not limited to:
- Culture smear microscopy
- Rapid test for isoniazid, rifampicin and fluoroquinolone resistance
- First and second line drug resistance testing

- Rapid molecular diagnostics (eg. Hain and GeneXpert)
- Nucleic acid amplification testing.

Hair
-Stored for future studies

7   DATA MONITORING AND QUALITY ASSURANCE
7.1   Statistical and Data Management

Prior to enrollment, all research staff will participate in human subjects protection training/Good Clinical Practice training to ensure sensitive data confidentiality for all study participants. Informed Consent Forms and all forms containing patient identifiers will be kept separate from study forms in a secure, locked location. Upon enrolment, participants will be assigned a unique study identifier (PID) assigned by the CAPRISA Data Management Center. Data will be collected by chart abstraction. Baseline (enrolment), Monthly Clinical Visits, and Follow-up Interviews will be collected with paper data collection forms (Case Report Forms (CRFs)). The PID will be used on all CRFs to identify the participant for the duration of the study.

Prior to recording any study data on paper-based CRFs, approval and instructions will be given by the CAPRISA Data Management core. Completed CRFs must be checked by an on-site Quality Control (QC) officer and upon approval, must be submitted via fax into the DataFax system. CAPRISA Data encoders and Data Managers located at the K-RITH Tower building will verify and validate patient data. Quality control reports are produced, and approved then added to the study database according to CAPRISA data management Standard Operating Procedures (SOPs).

DataFax software will be utilized for the development of study forms, and for data entry and data management in electronic format. The current version is version 4.1. Electronic data will be kept securely on encrypted and password protected end point devices with support from the CAPRISA Data Management Core. Only the Principal Investigators or designee will have access to the key linking the de-identified data to patient identifiers.

7.1.1   CAPRISA Data Management Core

The Data Management Core comprises 3 components; a) IT section, b) DataFaxing, data entry and data encoding and c) data management. Skills, technical support and infrastructure to enable quality data collection and efficient transfer of data from the sites to the data management center are available through the CAPRISA data management core. They are also responsible for purchase and maintenance of all data management equipment such as the DataFax machines.

7.1.2   Quality Control/Assurance

Quality checks will be performed on the paper-based study forms prior to DataFaxing. The QC procedures will include the following:

-No handwritten items are illegible.
-Responses are clearly documented within designated spaces.
-All fields are completed with participant data; if no data was available, this is specified.
-The participant PID is recorded on all pages of the study forms.
-The CAPRISA laboratory manager will ensure that all involved laboratories are compliant with Good Laboratory Practices (GLP).
- The CAPRISA pharmacist will provide oversight for the preparation of the electronic pillboxes and pill counts.

QA/QC of data will be undertaken according to CAPRISA SOPs.

7.1.3   Electronic Data Storage

CAPRISA It is the responsibility of the CAPRISA data management core to assure the quality of computerized data for the study. Study staff will be trained in source documentation requirements in accordance with the study SOP for Source Documentation and in proper forms completion techniques.

Database files will be password-protected, and access to the files will be limited to authorized study staff members only. Quality control and validation checks will be performed and data cleaning steps will be undertaken prior to finalizing the study database for analysis. Analyses will be conducted by study statisticians.

7.1.3.1 Long Term Data Storage

Original and DataFax electronic copies of study CRFs and related documents will be stored securely both during and after study completion. During the study, the original completed forms for each participant will be kept on-site at the CAPRISA KDH site. The forms will be stored in an access secured, double-locked room. Upon completion of the study, and finalization of the database for analysis, the original forms will be bound and kept off-site (separate site) for long-term storage. Personal information collected in this study will be archived in accordance with applicable guidelines and laws, including the Protection of Personal Information Act, 2013. CAPRISA has a standing agreement with a document storage company to archive large amounts of documents. CRF data on the DataFax server will be accessible to the study staff and the statistician in a read-only mode. The data management team will have write-access, with access being restricted by passwords and validation levels. Study staff that has access to the data on the computer systems will be trained in how to access the system and the importance of system security. All information will be backed-up at regular intervals, and backups will be stored in file cabinets or secure areas with limited access

Columbia University Medical Center Data transported to Columbia University will be sent as coded with the PID. Only the South African PI will have access to the key. Study personnel at Columbia University will not have access to identifying or sensitive patient data at any point. Study data will be kept in electronic format and will be kept confidential in accordance with Columbia University Medical Center guidelines http://www.columbia.edu/acis/security/users/index.html.

7.2 Instructions for Biological Specimen Management

Maximal infection control precautions will be taken by the research team members during specimen collection and preparation including use of double gloves, safe venipuncture equipment and a fit-tested N-95 respirator during sputum induction. Specimens will be collected in designated containers and labeled with a printed, bar coded labels that contain the patient identification number, the study visit, the specimen type, the intended assays and the specimen destination. Specimens for testing at the commercial laboratories will be directly transported there by courier.

Specimens for processing at the CAPRISA laboratory will be placed on ice and transported by courier to the CAPRISA laboratory where they will be appropriately aliquoted.

7.2.1 Biohazard Containment and Specimen Shipment

All specimens will be labeled by bar code and identifiable by PID. A specimen tracking log (including attestation of appropriate temperature maintenance during transport) will be utilized to document all transport of specimens between sites.

Transmission of HIV and other pathogens can occur through contact with contaminated needles, blood, blood products, and other secretions, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and collection of other specimens and shipping and handling of all specimens for this study, in accordance with guidelines by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

7.2.2 Future Use of Stored Specimens

A portion of the blood or sputum may be frozen and kept at CAPRISA for future tuberculosis research. Hair samples will be stored at room temperature in a dark location. A portion of these specimens may be kept for 10 years for assays developed in the future in accordance with NIH polies and practices.

Specimens will be stored confidentially with the bar coded patient identifier, separately from the key or any other identifying or sensitive patient information. The Biomedical Research Ethics Committee will monitor and provide permission for their ethical use in the future.

Specimens may be shipped at a later date. The appropriate regulatory documents will be completed and submitted prior to shipment.

DATA ANALYSIS

7.3 Power Calculations

Specific Aim A: The study sample will include 200 consecutively recruited patients meeting inclusion criteria. Data from 2010-2014 indicate that 1100-1400 newly diagnosed MDR-TB or XDR-TB patients registered for treatment per year (1). In previous studies we have prospectively enroll approximately 50% of eligible patients. Of these 80% will be HIV co-infected (30). Conservatively we expect to enroll 200 M/XDR-TB HIV patients, completing enrolment by 24 months.

Table 1. *Hypothesis 1a.* Power for differences between ART and TB medication percent adherence

	Difference in percent adherence		
Sample Size	**10%**	**15%**	**20%**
120		70	97
160		80	>99
200	54	93	>99
300	74	>99	>99
340	80	>99	>99
400	87	>99	>99

*Assuming 20% of the cells had discordant results
#Using an exact sign test of equality of paired proportions

Hypothesis A is powered to detect a differential adherence between ART and TB medications using differences seen in preliminary data as our assumptions. If we assume α set at 0.05, then a sample size of 200 will have 93% power to detect a difference in proportions of 0.15 when the proportion of discordant pairs is expected to be 0.20 and the method of analysis is a sign test of equality of paired proportions with a 0.05 two-sided significance level (Table 1).

Specific Aim B: From a subset of study participants enrolled in Aim 1a and healthcare workers, 80 partipants will be recruited for Aim 1b. Due to the qualitative and exploratory nature of this Hypothesis, no formal sample size calculations will be employed.

7.4 Hypothesis A

Average adherence and cumulative adherence through six months will be calculated (30). Descriptive statistics will be calculated using standard methods. Associations will be tested with Fisher's exact test. We will compare cumulative and average adherence for ART and second-line TB medications using a paired t-test (McNemar) (30). To identify sociomedical risk factors associated with six-month adherence to ART or TB medications we will first identified risk factors associated with adherence in bivariate analysis and then constructed multiple logistic regression models including variables which are statistically significant and/or associated with >10% change in effect measure. Interaction between terms will be assessed for significant change of the risk estimate. Test for trend will be performed using Cochran-Armitage test. Statistical analysis will be performed using SAS Version 9.3 (SAS Institute, Cary).

7.5 Hypothesis B

Analytic steps will be discursively applied, and include: 1) open coding, where transcribed data are broken into units of meaning to identify tentative codes; 2) axial coding, where codes are constantly compared across the dataset to identify the relationships between them and to derive core codes; and 3) selective coding, where core codes are reapplied to transcripts toward the organic identification and development of salient themes, latent patterns and negative cases (92, 94, 95). Codes will be applied iteratively, with transcripts reviewed multiple times for coding clarity and thematic development. A coding dictionary and analytic memos will be scrutinized to identify latent

patterns and negative cases, that is, points of convergence and divergence within group norms (86, 92). Inductive coding, using a grounded theory framework, will be substantiated by deductive coding, based on key constructs of the sIMB model (96). Qualitative findings will be triangulated with objective data (50) from Aim 1 to present a comprehensive characterization of adherence and retention in M/XDR-TB and HIV (45, 97).

9   HUMAN SUBJECTS PROTECTIONS

9.1 Ethical Considerations

Following approval of the protocol by the USAID review committee, the protocol and accompanying documents will be submitted concurrently to the HRPO IRB at Columbia University and BREC ethics boards.

The study will be conducted in compliance with South African, US, national and local regulations and guidelines applicable to research involving human subjects, and in accordance with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP). Should regulations and guidelines differ between countries, the more restrictive regulations and guidelines will apply. The protocol, informed consent forms, and study materials to be completed by study participants will be reviewed by the ethical review boards at Columbia University and CAPRISA. Modifications to any study materials will be submitted to regulative authorities as necessary and on an ongoing basis.

9.2 Human subjects considerations

The investigators are committed to the protection of the rights of all participants in the proposed research, in accordance with USAID policy. Prior to study enrolment, all research staff will be trained in principles of human subjects protection and management of confidential study materials. Study consent forms and protocols, including intervention materials, questionnaires, and data abstraction tools will be approved by the Human Research Protection Office Institutional Review Board (IRB) at Columbia University Medical Center and BREC.

> 9.2.1   Exclusion of Subpopulations. Children under the age of 18 will be excluded. It is likely that factors associated with ARV and TB medication initiation and retention in children will vary from that of adults and subsequently would obscure the sensitivity of the analysis.

> 9.2.2   Vulnerable Populations. Pregnancy is an exclusion criterion for this study as risks associated with drug resistant TB treatment are different for pregnant women. Prisoners will excluded from this study.

9.3 Informed Consent Process

Only participants providing informed consent per IRB/IEC requirements will be enrolled in this study. A member of the study staff will explain the protocol and informed consent documents prior to obtaining informed consent in the preferred language of the potential participant (English or isiZulu). The informed consent document contains information on the study purpose, study protocol,

possible risks/discomforts, possible benefits, alternatives, confidentiality, compensation for participation, rights (including the right to withdraw from the study), and will provide contact information to the study stuff and human protection offices. Potential participants will have the opportunity to discuss the protocol and address questions with a member of the study staff. Participation in the study is voluntary and refusal to participate will not affect the quality of care that individuals receive. Participants will be informed that he or she may withdraw from the study at any time. Withdrawal will not affect the quality of care that he or she receives.

When the potential participant fully understands the details of the study, his or her rights and responsibilities and expresses a wish to participate, the participant and the person explaining consent will sign and date the informed consent form. The person will be provided with a copy of the consent form as a record. If the participant chooses to withdraw at any time, he or she may simply contact the PI or person obtaining consent.

9.4 Confidentiality

Every effort will be made to ensure that participant information will remain confidential and, to the extent permitted by applicable laws and/or regulations will not be made publicly available. To prevent breaches of confidentiality, participants will be coded by a patient identifying number. Personal and identifying information will be kept separately and securely from study forms and study databases. Only the South African PI and specific collaborators will have access to the data key and identifier-containing documents. In accordance with the law, data may be reviewed by representatives of the IRB/IEC and individuals tasked with duties of monitoring and quality assurance.

Paper forms used to collect study data will be stored in secure locked cabinets. Data from questionnaires and study materials will be entered into electronic databases. Both paper study forms and electronic database data will be identifiable only by participant ID. Electronic databases will be stored on encrypted and password protected endpoint devices in accordance with guidelines. Study staff will be the only persons with access to the study database and paper records.

9.5 Quality Assurance

The study will be conducted in compliance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements in South Africa. All relevant study documents, including recruiting materials, informed consent documents and the protocol will be approved by the local ethics board. Quality Assurance site visits will be conducted by CAPRISA's Quality Assurance team, to ensure compliance with applicable regulations and ethical standards regarding protocol compliance, completion of informed consent procedures, eligibility verification, source documentation collection and maintenance, and CRF completion, as necessary.

The study coordinators based in South Africa and US will hold bi-weekly teleconferences with members of the Quality Assurance team to review data and procedures. Additional external monitoring will occur quarterly by Dr O'Donnell and the US-based Study Coordinator. External monitoring will include review of all study documentation, collected data and study team

performances. QC reports will be available from the CAPRISA Data Management Core, which will be reviewed periodically.

9.6 Potential Risks and Protections

This study is of minimal risk. There is no intervention associated with this study; this study involves answering questions about the standard care that participants receive and increased monitoring of adherence to both TB medications and ARVs. Below are possible risks associated with participating in the study and protections against them.

Loss of confidentiality: There is a risk of loss of confidentiality of information provided by participants during the course of the study, including focus group discussions. Every effort will be made to keep study participants' identifying information confidential. Personal identifiers (including name, address) will be kept in a separate and secure location from data collected for the purpose of the study. Participants will be provided with a study ID; only the South African PI and will have access to the key to decode the study ID.

All study forms will be identified with only the study ID. Study documents will be accessible only by study personnel and will be kept securely in locked cabinets. Study databases will be kept on encrypted and password protected end point devices in accordance with privacy guidelines.

Staff will be trained prior to the start of this study with periodic refresher training to ensure compliance with privacy principles and laws.

Risk of Discomfort: Study participants will be asked to participate in monthly interviews and complete questionnaires for a 6-month period. A subset of study participants will participate in focus group discussions about their treatment. Questionnaires and FGDs require participants to answer questions regarding their personal barriers and facilitators to treatment adherence, including sociodemographic, clinical and behavioral determinants. These discussions and questionnaires may be uncomfortable. Study staff trained in facilitation of questionnaires and focus group discussions will conduct these interviews. Study staff will be trained with communication and interview skills to address and navigate potential stressors and discomfort. In accordance with the informed consent, participants will be instructed that they are not required to disclose any personal or uncomfortable information and may withdraw from the study at any time.

As this study requires blood samples to be drawn, there is a risk of discomfort. There is a risk of mild pain, local irritation, bleeding or bruising at the puncture site. There is a small risk for light-headedness and/or fainting.

This study will require that hair samples be collected. There is a minimal risk of discomfort or that the participant's skin could be inadvertently cut during the process.

9.7 Potential Benefits

There likely will be no direct benefit to patients for participating in this study. Increased adherence monitoring and participation in focus group discussions will allow study stuff to better understand the barriers and facilitators to adherence to both ARVs and TB medications. This knowledge may help investigators to improve treatment support and programs for patients in the future.

9.8 Alternatives

Taking part in this study is voluntary. If potential participants decide not to take part in the study he or she will not lose any of the regular benefits. Tuberculosis treatment is provided without cost in accordance with the South African TB Program (NTP) guidelines. If the participant decides not to continue this study, he or she may leave the study at any time without penalty. Leaving the study will not affect the standard of medical care.

In the case of participation in focus group discussions by health health care professionals, declining to participate or leaving the study will not affect his or her professional standing.

9.9 Adverse Events Reporting

The risk of adverse events is low for participating in this study as there is no interventional aim in this study.

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily has to have a causal relationship with this treatment. All adverse events will be documented and reported to the PI. Study related serious adverse events will be reported to the proper Ethics Committee in accordance with regulations. The study team will discuss adverse events as they occur and steps to prevent recurrence.

An adverse event may include the loss of electronic data, paper-based data, or other potentially sensitive or identifying information. The Columbia University Medical Center Human Research Protection Office (HRPO) Institutional Review Boards (IRB) and BREC will be informed of potential privacy breaches in accordance with reporting guidelines.

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