PROTOCOL

Adaptive evaluation of mHealth and conventional adherence support interventions to optimize outcomes with new treatment regimens for drug-resistant tuberculosis and HIV in South Africa

Version 1.0, 8 April 2022

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Acronyms

ART	Antiretroviral Therapy
AIDS	Acquired Immunodeficiency Syndrome
BAR	Bayesian adaptive randomization
BDQ	Bedaquiline
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)
DR-TB	Drug resistant tuberculosis
DSD	Differential Service Delivery
FGD	Focus Group Discussion
GCP	Good Clinical Practice
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
MDR-TB	Multi-drug resistant tuberculosis
MMAS-8	Morisky Medication Adherence Scale
M/XDR-TB	Multi-drug resistant tuberculosis or Extensively drug resistant tuberculosis
MI	Motivational Interviewing
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
TLD	Tenofovir/lamivudine/DTG Combination Pill
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	United States Agency for International Development
VAS	Visual Analog Scale
WHO	World Health Organization

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INVESTIGATOR SIGNATURE FORM
Version 1.0
08 April 2022

Funded by:
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I, the Investigator of Record/Principal Investigator, agree to conduct this study in full accordance with the provisions of this protocol. I have read and understand the protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Principal Investigator

Signature _____ 14/Apr/22

Date of Signature (DD/MMM/YY)

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1 STUDY OVERVIEW

Adaptive evaluation of mHealth and conventional adherence support interventions to optimize outcomes with new treatment regimens for drug-resistant tuberculosis and HIV in South Africa

1.1 Summary

The availability of shorter, more effective, entirely oral bedaquiline (BDQ) containing drug-resistant tuberculosis (DR-TB) treatment regimens (1), and highly potent, low drug-drug interaction profile, integrase strand transfer inhibitor (INSTI)-based combination ART have transformed the treatment paradigm for DR-TB HIV (2-4). However, without similar ground-breaking advances in adherence support, we will not realize the potential of these revolutionary therapeutics and novel regimens may rapidly lose their benefits due to emergent resistance to either antimycobacterial agents and/or antiretrovirals (5, 6).

1.2 Background

Tuberculosis (TB) is now the second leading cause of death due to a single infectious agent (7), recently displaced by SARS-Cov-2 (8). TB remains the single leading cause of death for persons living with HIV/AIDS (9). Although TB incidence is slowly decreasing (7, 10), global End TB 2020 incidence and mortality milestones were not achieved (11). An important reason for this missed opportunity is an increase in DR-TB cases with high mortality and poor treatment outcomes (12, 13). Approximately ~820,000 incident TB cases globally occur in HIV co-infected patients (7). The majority (59%) of TB patients in South Africa with known HIV status are co-infected (14, 15), and there are ~14,000 incident DR-TB HIV cases per year (7). South Africa has ~18% of global MDR-TB burden and the highest number of DR-TB HIV cases (7, 16, 17).

Medication adherence, a key predictor of outcomes in DR-TB and HIV treatment, is understudied in high burden TB-HIV settings (18-20). Patient losses during transitions in the care continuum are frequent (21), increase mortality and limit control of the linked epidemics. Demands of DR-TB HIV treatment are severe including extraordinary pill burden, severe adverse effects, lengthy treatment, isolation, and stigma with few parallels in modern medicine (22-24).

1.3 Specific Aims

Aim 1. To compare the effect of a multi-arm adaptive adherence intervention on DR-TB HIV outcomes

Aim 1 overview. This Aim seeks to use an adaptive implementation platform to randomize DR-TB HIV patients initiating BDQ and TLD to compare the effect of different interventions on biological and clinical endpoints (*1a*) and determine BDQ threshold adherence value associated with DR-TB culture conversion (*1b*).

Hypothesis 1a *In a randomized, adaptive implementation trial, the psychosocial + mHealth support arm will improve a composite DR-TB HIV clinical outcome compared to separate mHealth, psychosocial support, or enhanced standard of care arms. (N=360)*

Hypothesis 1a overview. This study aims to evaluate the impact of different adherence support elements informed by a DSD framework in patients with DR-TB HIV. Specifically, in this hypothesis we will use a four-arm, adaptive randomized design to study the impact of adherence support interventions on clinical outcome. The four arms will include: enhanced standard of care (ESOC) (I), psychosocial support (II), mHealth (III), psychosocial support + mHealth. Components of the intervention have been informed by preliminary qualitative research that elucidated critical patient needs at key stages in DR-TB HIV treatment.

Aim 1 Hypothesis 1b *Quantitative adherence measurement using EDM will define BDQ adherence thresholds that are more predictive for TB outcomes than conventional adherence measures. (N=180)*

Hypothesis 1b overview Medication adherence is widely considered to be a critical determinant of response in the treatment of infectious pathogens - including *M. tuberculosis* - but is severely understudied. For BDQ, quantitative adherence thresholds sufficient to ensure TB culture conversion at 6 months and optimal end of treatment clinical outcome are not known.

1.4 Methods

The overall structure is a 4-arm adaptive platform of mHealth and psychosocial adherence support interventions informed by a *differentiated service delivery* (DSD) approach. The framework is a study of mHealth and psychosocial adherence support interventions using a Bayesian adaptive design to allow comparison of elements of the intervention separately and in combination.

Participants will be randomized into one of 4 arms and followed monthly through the 6 months of intervention, then through the end of treatment telephonically, with an additional in-person visit to establish the primary outcome. Primary outcome is a combined clinical/biological outcome at 12 months described below. *Hypothesis 1a* utilizes all participants while *1b* utilizes only those in the mHealth intervention arms (3+4) since granular EDM-measured adherence is required. Detailed methods are described in section 4.3 below.

1.5 Population

Eligible patients will be consecutively recruited adult patients (age ≥ 18 years) presenting with all of the following inclusion criteria: (1) Culture or molecular test positive for MTB, (2) Molecular test positive for HIV or a documented HIV positive history (3) Drug-susceptibility testing by molecular (i.e. GeneXpert MTB/RIF) or conventional testing consistent with at least rifampicin-resistant TB, (4) Initiating treatment with a BDQ-containing TB regimen within 4 weeks of enrollment and first-time being treated with BDQ (5), On treatment with ART regimen, including dolutegravir-containing combination ART regimen (i.e. TLD), or starting within 4 weeks of enrollment, (5) Capacity for informed consent in either isiZulu or English.

Patients will be excluded from the study if they are prisoners, and if they are pregnant on enrollment. Patients will be recruited from King DinuZulu Hospital, a centralized TB referral

hospital near Durban, South Africa which initiates the majority of BDQ treatment regimens in the province, and/or referral clinics for King DinuZulu Hospital.

1.6 Study Duration

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

1.7 Participant Duration

Study visits will occur monthly until 6 months with a follow-up visit at 12 months. A telephonic visit will occur at the end of treatment (9 to 18 months after treatment initiation DR-TB). See Schedule of Evaluations for further details.

1.8 Potential Significance

The availability of shorter, more effective, oral bedaquiline (BDQ) containing drug-resistant tuberculosis (DR-TB) treatment regimens (1), and highly potent, low drug-drug interaction profile, integrase strand transfer inhibitor-based combination ART have transformed the treatment paradigm for DR-TB HIV (2-4). However, without similar ground-breaking advances in adherence support, we will not realize the potential of these revolutionary therapeutics and novel regimens may rapidly lose their benefits due to emergent resistance to either antimycobacterial agents and/or antiretrovirals (5, 6).

The NIAID has identified improved treatment of DR-TB and TB/HIV as a research priority (25). The proposed research will increase *local scientific capacity* in South Africa and train local investigators, including women and minorities (26). Successful completion of our Aims will substantially advance our understanding of DR-TB and HIV adherence dynamics in an integrated research strategy n land program and develop an innovative set of tools for the assessment and support of dual TB and ART medication adherence. *Conceptually*, our work will advance the *differentiated service delivery* model into DR-TB HIV treatment. *Practically*, we will evaluate components of adherence support using an adaptive platform to determine the effectiveness of mHealth and psychosocial support (*Aim 1*). We will characterize potential intervention mechanisms of action by measuring model-based socio-behavioural variables and contextualize the longitudinal intervention impact in key stages of DR-TB HIV treatment using qualitative methods.

The study findings may be used to inform programmatic management and the development of further interventions that promote adherence for DR-TB HIV patients.

2 PERSONNEL AND TRAINING

2.1 Roles

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

Dr. O'Donnell with Dr. Naidoo 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.

Dr. Cheung will lead a training on the randomization strategy and software use. Study staff assigned to randomization duties will participate in training prior to study initiation.

Supervision will be provided to ensure participant safety and good study conduct.

Enhanced standard of care (Arm 1) will include usual care as administered by hospital and clinic staff enhanced by study staff-provided treatment literacy and study-provided training for treating physicians, nurses, pharmacists, and social workers prior to study initiation and periodically with refresher trainings

3 BACKGROUND AND SIGNIFICANCE

Tuberculosis (TB) is the leading cause of mortality for people living with HIV, causing over 200,000 deaths annually (7). Approximately 860,000 incident TB cases occur in HIV co-infected patients worldwide (27). In southern Africa, interaction between TB and HIV epidemics has led to increased community transmission of drug-resistant TB (DR-TB) (17, 28-30),critically undermining TB and HIV-related treatment goals (31, 32).

In South Africa, there are approximately 14,000 incident DR-TB HIV cases per year (7). Antiretroviral therapy (ART) in DR-TB HIV is challenged by older regimens and drug-drug interactions. Dolutegravir, an integrase strand transfer inhibitor, formulated as once-daily combination ART (tenofovir/lamivudine/dolutegravir (TLD)) (33, 34), is recently available in South Africa (35). TLD is superior to older comparator regimens, protective for ART discontinuation, and proposed as first-line ART including for treatment of DR-TB HIV (36, 37), but adherence in this context is not well studied.

Medication adherence is a key predictor of TB treatment outcomes and emergent drug-resistance (38-40), and is severely understudied in high burden TB/HIV settings (41, 42). DR-TB HIV treatment demands are daunting, including high pill burden, adverse effects, lengthy treatment, and stigma (23, 43, 44) with challenges in key treatment stages (45, 46). Bedaquiline (BDQ), a highly effective antimycobacterial, is the first new DR-TB drug in 40 years, and WHO-recommended as a key component of all new DR-TB treatment regimens (1, 47). Research by our team in South Africa, shows high mean BDQ adherence in DR-TB HIV measured using cellular-enabled EDM (48). However, a substantial adherence challenged subgroup (~16% patients) is at high risk for treatment failure, mortality, and emergent bedaquiline resistance (1, 49).

Patient-centered adherence support strategies using psychosocial support and mHealth (health practices supported by mobile technologies and devices) may improve DR-TB HIV outcomes. These modalities have improved medication adherence in HIV (50-55), hypertension (56, 57), diabetes (58), and psychiatric disease (59-61). Our team has done important early work in mHealth adherence support and comprehensive psychosocial support for DR-TB HIV (48, 62). A critical gap, addressed by our proposal, is to understand the relative contributions of mHealth and psychosocial adherence support to improve clinical and biological outcomes in DR-TB HIV treatment.

Differentiated service delivery (DSD) is an innovative person-centered care model tailored to the health status and clinical needs of persons living with HIV/AIDS, informed by social, behavioral and structural factors (63-65). DSD methods include *mHealth* (health practices supported by mobile technologies), psychosocial support, and community-based care (65, 66). We have piloted mHealth-guided adherence support in DR-TB HIV treatment in South Africa, using electronic dose monitoring (EDM) to measure real-time adherence (48).

For our study in, we use an adaptive design including patient-centered care concepts derived from DSD. Using elements of the DSD approach within each of the 3 intervention arms (excluding

the enhanced standard of care arm) the intensity of each intervention will be calibrated based on empirically determined participant requirements. DSD evaluation will be performed by incorporating monthly questions regarding DSD acceptability and patient preference, intensity of DSD inputs will be recorded, but due to limited resources a statistical power stratified analysis by DSD will not be performed.

The burden of stigma for patients with DR-TB/HIV Stigma was initially described by Goffman as a “deeply discrediting” attribute understood through a “language of relationships” and social interactions (67). Contemporary scholars have called attention to social interactions, structures and practices that set up normative expectations about what is acceptable versus devalued (68, 69). Stigma characterizes the lived experience of HIV and is acknowledged as a key obstacle to global HIV control (69). Health activists and persons with HIV have confronted HIV stigma (70) to protect patients from systemic discrimination (71). Persons with TB have long been stigmatized due to their association with poverty and the fear of contagion (72, 73). High rates of HIV co-infection in countries such as South Africa and emergence of nearly untreatable DR-TB, have renewed fears about TB patients leading to new forms of TB-HIV stigma (71, 74, 75). Intersectional DR-TB/HIV stigma has been identified by our group as an important obstacle to treatment success (76).

4 STUDY OBJECTIVES AND AIM

4.1 Rationale

Improved treatment of drug-resistant tuberculosis and HIV has been identified as a research priority (25). 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 (26).

We will implement an adaptive trial for improving adherence and retention. We will explore the impact of the intervention on reducing barriers and improving facilitators to adherence and qualitatively explore the feasibility and acceptability of an integrated intervention for adherence and retention in care. We will carry out this work in the inpatient setting by expanding the standard of care and focusing on the transition to outpatient care. We will also extend the intervention to focus on the outpatient community setting where patients may have the greatest adherence challenges and highest likelihood of treatment default.

4.2 Specific Aim and Hypotheses

Aim 1 overview. This Aim seeks to use an adaptive implementation platform to randomize DR-TB HIV patients initiating BDQ and TLD to compare the effect of different interventions on

biological and clinical endpoints (*1a*) and determine BDQ threshold adherence value associated with DR-TB culture conversion (*1b*).

Aim 1. To compare the effect of a multi-arm adaptive adherence intervention on DR-TB HIV outcomes Using a 4-arm Bayesian, adaptive trial design (77), we will prospectively evaluate adherence support components in DR-TB HIV patients treated with BDQ and TLD. The primary outcome will be a composite of HIV viral load, TB culture conversion, survival, and retention in care at 12 months. Within each intervention arm, required adherence support will be empirically determined and delivered using a DSD framework.

Hypothesis 1a *In a randomized, adaptive implementation trial, the psychosocial + mHealth support arm will improve a composite DR-TB HIV clinical outcome compared to separate mHealth, psychosocial support, or enhanced standard of care arms. (N=360)*

Aim 1 Hypothesis 1b *Quantitative adherence measurement using EDM will define BDQ adherence thresholds that are more predictive for TB outcomes than conventional adherence measures. (N=180)*

5 METHODS

5.1 Overview

Time line

Dates are approximate

- 6 months for staff training
- Obtain regulatory and ethical approvals
- Approximately 36 months for enrolment (360 patients)
- Participants will be followed monthly until 6 months
- Follow-up visit at 12 months
- End of treatment telephonic visit

Overview of Study Processes (see 6.1 Schedule of Study Evaluations)

All participants

- Informed consent
- Baseline (Intake) Assessment
- Social and Medical history, etc.
- Monthly and Follow-up Assessments
- Sputum and blood collection
- Collect HIV viral loads, sputum cultures through routine clinical care
- Collect monthly pharmacy records
- Determine clinical end of treatment outcome

Arm 1 Enhanced Standard of Care

- Usual clinical care enhanced by:
- Treatment literacy counseling
- Monthly physician visits
- Social work and other services initiated routinely
- Study team provides extra training for physicians, nurses and social workers to enhance standard of care

Arm 2 Psychosocial Support

In addition to Arm 1:

- Discharge planning (if inpatient)
- Community treatment planning (if outpatient)
- Individual counseling
- Community adherence support group
- Home visits*
- Monthly TB adherence assessment questionnaire (MMAS-8)**

Arm 3 mHealth

In addition to Arm 1:

- Weekly text messaging*

- Wisepill RT2000 devices: one or bedaquiline and one for TLD
- Troubleshooting phone calls for detected non-adherence*
- Weekly assessment of adherence measured by the Wisepill RT2000 device[$]

Arm 4 Psychosocial support + mHealth
Combination of Aims 2 and 3**[$]

*These elements may be increased in intensity or frequency depending on empirically assessed patient needs within each arm
**If the participant has a Morisky Medication Adherence Scale (MMAS-8) score <6 he/she will be considered 'at-risk' for non-adherence and will have the intensity of the intervention increased in the following stepwise fashion: A) Telephonic check in by study staff B) Increased frequency of counselling sessions from monthly to biweekly C) home visit by a multidisciplinary study team.

[$]Less than 85% observed/expected doses will be considered at risk for non-adherence and will have the intensity of the intervention increased in a stepwise fashion: A) Telephonic check in by study staff B) Increased frequency of text messaging from weekly to daily.

5.2 Study Design

This study will follow a 4-arm Bayesian, adaptive trial design. As patients are enrolled, they will be randomized into one of the four arms.

The study will be carried out within a common structure to allow for efficient enrollment and analysis. The overall structure is a 4-arm adaptive platform of mHealth and psychosocial adherence support interventions informed by a differentiated service delivery (DSD) approach.

Aim 1 is an adaptive study of mHealth and psychosocial adherence support interventions using a Bayesian adaptive design to allow comparison of elements of the intervention separately and in combination. Aim 1 participants will be randomized into one of 4 arms and followed monthly through the 6 months of intervention, then through the end of treatment telephonically, with an additional in-person visit to establish the primary outcome. Primary outcome is a combined clinical/biological outcome at 12 months described below. Hypothesis 1a utilizes all participants while 1b utilizes only those in the mHealth intervention arms (3+4) since granular EDM-measured adherence is required.

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 (78, 79).

5.4 Recruitment

This is a prospective interventional cohort study for people with HIV that have been diagnosed with DR-TB and are initiating treatment at King DinuZulu Hospital (KDH), a centralized TB referral hospital in Durban, South Africa, which initiates the majority of BDQ treatment regimens in the province. Eligible patients include those from referral clinics for King Dinuzulu Hospital. Consecutive patients meeting inclusion criteria will be approached 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 Inclusion Criteria

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 rifampicin resistance **OR**
Polymerase chain reaction test (Xpert MTB/RIF) result showing MTB positive and RIF resistance.

3) Initiating treatment for DR-TB which includes Bedaquiline (BDQ) containing TB regimen within 4 weeks of enrollment and first-time being treated with BDQ

4) Have capacity for informed consent

5) Molecular test positive for HIV or a documented HIV positive history. On treatment with ART regimen, including dolutegravir-containing combination ART regimen (i.e. TLD), or starting within 4 weeks of enrollment, as per clinician recommendation

5.4.2 Exclusion Criteria

Pregnancy
Prisoners
Discretion of IOR or clinician

5.5 Randomization Strategy

Eligible participants will be assigned to one of four intervention arms at baseline using a two-step randomization. In the first step, participants will be randomized to (Arm 1) vs (Arms 2-4) in a 1:3 ratio, using a minimization method to achieve balance over the following baseline stratifying variables: inpatient vs. outpatient treatment; MDR-TB vs. higher level MTB drug resistance; baseline CD4 T-cell count >200. In a second step, a Bayesian adaptive randomization (BAR) scheme will be used to further randomize the DSD participants to one of three DSD arms: psychosocial support (Arm 2), mHealth support (Arm 3), or mHealth + psychosocial support (Arm 4) based on the posterior distribution of the success rates of the three arms. Specifically, the randomization probability to an arm will be proportional to posterior probability that arm has the highest success rate (80, 81). For example, the randomization probability to Arm 2 (psychosocial support alone) will be calculated as $\boldsymbol{Prob\ (P_2 > P_3\ and\ P_2 > P_4 \mid data)}$, where P_2, P_3, P_4 denote the success rates of achieving the combined treatment outcome; in Arms 2, 3, 4 respectively, and data are updated continuously throughout the study. Under this randomization scheme, **90 participants** will receive ESOC and **270 participants** will receive random allocation among the three arms (**360 participants total**). In addition, we will adopt some practical implementations of the BAR scheme. First, we will apply an initial run-in period in which DSD participants will be assigned with equal probability to the three arms. The run-in period will end once the first 30

DSD participants have completed their 12-month evaluation. Second, while the primary endpoint is 12-month outcome, we will incorporate outcome at 6-months in updating the randomization probability during the study (81, 82). Third, web applications will be used to facilitate adaptive randomization in real time with up-to-date data. Intermediate outcomes at 6-month, the final 12-month combined treatment outcomes, and the stratifying factors will be updated on a continuous basis by the study coordinator via a data entry app. Randomization probabilities will be updated based on the updated data; and the study coordinator will obtain randomization code based on these updated probabilities via a randomization app.

6 DATA COLLECTION

6.1 **Schedule of Study Evaluations**

Procedures[+]	**Baseline (enrolment)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 12**	**End of Treatment (6-18 months)**
All Participants									
Informed consent	x								
Randomization to group (Arms 1-4)	x								
Treatment literacy counseling	x								
Baseline (Intake) Assessments	x								
Complete medical history chart abstraction	x	x	x	x	x	x	x	x	x
Follow-up Assessments		x	x	x	x	x	x	x	x
Early morning sputum sample collection for storage	x		x				x	x	
Blood Sample collection for storage	x		x				x		
Depression Screen	x						x	x	
Stigma Screen	x						x	x	

sIMB Questionairre	x						x	x	
Intervention groups only									
Arm 2									
TB adherence assessment (MMAS-8)		x	x	x	x	x	x	x*	
Monthly counseling intervention (MCI)[$]		x	x	x	x	x	x		
Adherence Support Groups (ASG)		x	x	x	x	x	x		
Home visits[&]	As needed basis								
Post discharge phone call (PDP)				Within 7 days post hospital discharge					
Arm 3									
Pill count by Wisepill electronic pillbox	Daily from time of randomization into intervention arm until discharge from study.								
TB adherence assessment (Wisepill)		x	x	x	x	x	x	x*	
Issue Wisepill device, training	Within 14 days post-randomization into the intervention arm.								

Adapted Wisepill Intervention (AWI)	Intervention (phone call, home visits) triggered by non-adherence as detected by Wisepill non-opening.
Arm 4	
	Will include all available interventional tools**

[+]Monthly pharmacy records will be obtained; Routine HIV viral loads, sputum culture results will be collected from the clinic
*If participant remains on treatment
[$]Frequency may increase based on need
[&]Participant may opt out. Timing and frequency based on the discretion of the investigator
**Arm 4 is the combination of each intervention. Participants that are randomized to Arm 4 will complete all tasks at each time point specified for Arms 1-3.

6.2 Study Data and Sample Collection

All participants

All participants will receive *Enhanced Standard of Care (*ESOC).

Enhanced Standard of Care:

ESOC will consist of care from trained and supported physicians, nurses, and social workers who have received repeated trainings from study staff on medical and behavioral aspects of DR-TB HIV care, which will be documented in terms of date, attendance, and content.

All participants who receive care as inpatients will receive an orientation to DR-TB treatment in form of a group session designed to impart key behavioral information and health knowledge about the disease, treatment, and skills to obtain optimal outcome.

All participants will receive pamphlets and informational materials designed to support the above goals.

All participants who receive care as inpatients will receive an exit counseling session scheduled prior to discharge where the PRAXIS staff will review key behavioral information and health knowledge about the disease, treatment, and skills as well as review challenges to reproducing care as an outpatient.

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.

Psychosocial support methods

Psychosocial support methods include individual counseling/case management, home visits (if warranted and consented to), and adherence support groups which can support patient motivation and provide information to assist behavioral change. Participants in arms 2 and 4 will participate in individual counseling aligned with their monthly clinic visit, or more frequently if indicated. Individual counseling will use motivational interviewing (MI) techniques, based on the 4-part engaging, focusing, evoking and planning approach for each participant to set goals and anticipate barriers to successful engagement in care (83). Counselors will be qualified mental health counselors or credentialed social workers trained in MI skills using validated training materials (84). If required, the same trained counselors known to patients would conduct home visits. To minimize potential stigma and increase confidentiality, home visitors would arrive in unmarked vehicles and discuss the visit only with the patient or agreed upon contacts. Participants in arms 2 and 4 will attend monthly, gender specific, structured adherence support groups. Adherence support groups will be facilitated by counselors trained in group facilitation methods; group curriculum will include 6 sessions that focus on practical topics including accessing social grants, economic stability, and family issues and will utilize guest speakers as

appropriate. Structured support groups have been used in patient-centered healthcare to address both support and information needs among similarly affected individuals (85). Gender specific groups have been found to promote open sharing and allow for focus on gender specific topics (86).

mHealth Methods

The portable Wisepill RT2000 cellular-enabled electronic pill boxes ('Wisepill') uses 2G/3G cellular network to automatically synchronize with the Wisepill Cloud service and was designed for use in research and clinical trials. Participants will receive 2 Wisepill devices and training on loading, charging and storage. One Wisepill will be designated and externally labeled for ART and the other device for BDQ, to avoid confusion. Pill box openings serve as a surrogate for adherence to ART (which may be either TLD, or NVP or LPV/RTV) and BDQ respectively. Each participant will select a text message reminder from a guided menu of choices and receive a weekly text message encouraging adherence. For >2 missed openings or openings outside of the programmed dose-window (not due to technical issues) the participant will receive a semi-scripted study call to support regular adherence. Participants will be assessed weekly using Wisepill percent adherence. Less than 85% observed/expected doses will be considered at risk for non-adherence and will have the intensity of the intervention increased in a stepwise fashion: A) Telephonic check in by study staff B) Increased frequency of text messaging from weekly to daily.

Reimbursement

Patients will be reimbursed for study visits at baseline, monthly 1-6 months, 12 months, and end of treatment.

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 community adherence support groups. 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.

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.

6.3 Biological Specimen Collection, Preparation, Handling and Shipping

6.3.1 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 month 2, 6, 12 additional specimen collection may include:

- 10 ml blood
- One sputum sample

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.

6.3.2 Laboratory Evaluations

Blood
-HIV viral load, biobanking for future studies including metabolomics, proteomics, and transcriptomics

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
- Pathogen whole genome sequencing

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. Relevant clinical data will be collected by chart abstraction. Baseline (enrolment), Monthly Clinical Visits, and Follow-up Interviews will be collected with tablet-based 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 capturing any study data into CRFs, instructions will be given by the CAPRISA Data Management core. Completed CRFs must be checked by the Quality Control (QC) officers. CAPRISA Data Managers will verify and validate patient data. Quality control reports are produced and approved per CAPRISA data management Standard Operating Procedures (SOPs).

RedCap software will be utilized for the development of study forms, data entry, and data management of electronic data. Electronic data will be kept securely on encrypted and password protected end point devices with support from the CAPRISA Data Management Core. Users on the study team will have access to the study database with individual login credentials including username and password.

Only the designed members of the study staff will have access to the key linking the study PID 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 data entered into the RedCap database.

-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

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 in accordance with federal (both NIH and US guidelines). Upon completion of the study, and finalization of the database for analysis, any original, paper-based 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 RedCap 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 study designees 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, barcoded 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 barcode 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 research. 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 barcoded 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.

8 DATA ANALYSIS

8.1 Power Calculations and Statistical Methods

Hypothesis 1a

The study is expected to enroll a total of 360 participants, who will be randomly assigned to one

of four intervention arms. Since retention in care is a component of the composite 12-month outcome, we expect that missing data will be minimal. Since 'missingness' will be part of the primary outcome (i.e., lack of retention in care or loss to follow up) patients who are 'lost' will actually provide important study data. A Bayesian adaptive randomization algorithm will be used to assign interventions to patients to improve the power of detecting any superior arm(s) and to increase the number of patients treated in the better arm(s) during the study.

Hypothesis 1a

Assuming EDM have an accuracy of 85% (for either positive and negative outcome) against a random guess (i.e., a null 50% accuracy), the statistical power for a one-sample binomial test (two-sided at 5% level) will be greater than 99% when the sample size available for this aim is 90; while we expect the sample size available for this aim will be random due to BAR and will be at least 180.

9 HUMAN SUBJECTS PROTECTIONS

9.1 Ethical Considerations

This protocol and supporting 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 Harmonization (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 ART 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. Informed Consent Process will begin with a concise and focused presentation of the key information about the research 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 procedures, possible risks/discomforts, possible benefits, alternatives, confidentiality, compensation for participation, and rights (including the right to withdraw from the study) and will provide contact information to the study staff 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 person obtaining consent or another member of the study team.

There will be a separate section detailing risks and benefits of permitting biobanking of serum/plasma for future studies including metabolomics, proteomics, and transcriptomics.

Participants will be be given the opportunity to decline participation in the biobanking component and still participate in the overall study.

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' identifying data will be coded to 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 the study team at CAPRISA 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. Electronic forms used to collect study data will be encrypted and accessible only through a password protected portal. 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. CAPRISA's Quality Assurance team will ensure compliance with applicable regulations and ethical standards regarding protocol compliance, proper completion of informed consent procedures, eligibility verification, source documentation collection and maintenance, and CRF completion.

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 drug or device intervention involved with this study. This study involves a behavioral intervention and increased monitoring of adherence to both TB medications and ART. Participants will answer questions about the standard care they receive. 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 throughout the course of the study. 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; all forms will use the PID for identification. Only the South African study team 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. Paper study forms will be kept securely in locked cabinets; electronic study forms will be secured on an encrypted and password protected study portal. Study databases will be kept on encrypted and password protected end point devices in accordance with privacy guidelines.

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

Risk of Discomfort: All participants will complete questionnaires at specified time points. Study participants in the intervention group will be asked to meet with a social worker at regularly scheduled clinic visits at month 2, 6, and 12. These questionnaires and discussions may be uncomfortable. Study staff trained in facilitation of questionnaires will conduct baseline interviews. Study staff will be trained with communication and interview skills to address and navigate potential stressors and discomfort. Social workers that conduct social work sessions will be trained in Y. 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.

9.7 Potential Benefits

Patients in each of the four arms will receive enhanced care. The goal of this study is to improve adherence and long-term outcomes through differential service delivery. There is no guarantee of a direct benefit received by taking part in this study. However, the knowledge gained may guide investigators in improving treatment support and programs for individual patients in the current study and 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.

9.9 Adverse Events Reporting

The risk of adverse events (AE) is low for participating in this study as there is no medicinal interventional in this study. However, as this study does include a behavioral intervention, AEs will be closely monitored.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the treatment. All adverse events will be documented and reported to the PI. Study related serious AEs 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 AE 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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