

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 (ADAP-TIV): Study protocol for an adaptive randomized controlled trial

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Research Article

Keywords: Tuberculosis, MDR-TB, HIV/AIDS, Bedaquiline, Antiretrovirals, mHealth, South Africa, Adherence support

Posted Date: June 9th, 2023

DOI: <https://doi.org/10.21203/rs.3.rs-2841179/v1>

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Abstract

Background Highly effective, short course, bedaquiline-containing treatment regimens for multidrug-resistant tuberculosis (MDR-TB) and integrase strand transfer inhibitor (INSTI)-containing fixed dose combination antiretroviral therapy (ART) have radically transformed treatment for MDR-TB and HIV. However, without advances in adherence support, we may not realize the full potential of these therapeutics. The primary objective of this study is to compare the effect of adherence support interventions on clinical and biological endpoints using an adaptive randomized platform.

Methods This is a prospective, adaptive, randomized controlled trial comparing the effectiveness of four adherence support strategies on a composite clinical outcome in adults with MDR-TB and HIV initiating bedaquiline-containing MDR-TB treatment regimens and receiving ART in KwaZulu-Natal, South Africa. Trial arms include 1) enhanced standard of care; 2) psychosocial support; 3) mHealth using cellular-enabled electronic dose monitoring; 4) combined mHealth and psychosocial support. The level of support will be titrated using a differentiated service delivery (DSD)-informed assessment of treatment support needs. The composite primary outcome will include survival, negative TB culture, retention in care and undetectable HIV viral load at month 12. Secondary outcomes will include individual components of the primary outcome and quantitative evaluation of adherence on TB and HIV treatment outcomes.

Discussion This trial will evaluate the contribution of different modes of adherence support on MDR-TB and HIV outcomes with WHO recommended all-oral MDR-TB regimens and ART in a high-burden operational setting. We will also assess the utility of a DSD framework to pragmatically adjust levels of MDR-TB and HIV treatment support.

Trial Registration ClinicalTrials.gov: NCT05633056 | December 1, 2022

Funded by The National Institutes of Health (NIH). Grant # R01 AI167798-01A1 (MO)

Background

Tuberculosis (TB) is the second leading cause of death, after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), due to an infectious agent and remains the leading cause of death for persons living with HIV/AIDS (1). Multi-drug resistant tuberculosis (MDR-TB) is defined as TB resistant to rifampicin and isoniazid, the two most potent bactericidal first-line antimycobacterial drugs (1). In 2021, there were an estimated 450,000 incident cases of people with MDR-TB globally, a 3.1% increase from 2020, with an estimated 191,000 associated deaths (1). The 2020 global milestones to reduce TB incidence by 20% and mortality by 35% were not achieved [1,2]; an important reason for this failure was an increase in the overall burden of MDR-TB.

Until recently, treating MDR-TB has required complex regimens with long duration and severe adverse events (3). Despite this, MDR-TB patients experienced low rates of treatment success and high attributable mortality (1,4). In 2012, bedaquiline, an oral agent for MDR-TB with a novel mechanism of

action, was licensed by the FDA, allowing for development of all-oral regimens. In 2020, the World Health Organization (WHO) recommended new shortened bedaquiline-containing MDR-TB regimens, following evidence of improved treatment success (3,5). An expanding body of evidence describes improved survival and lower treatment burden with oral short course MDR-TB regimens (6).

Among incident cases of TB, approximately 710,000, or 6.7%, were people living with HIV (1). In South Africa, the majority (53%) of TB patients are HIV co-infected (1,7). Advances in antiretroviral therapy (ART) regimens utilizing second-generation integrase strand inhibitors (INSTIs) have led to enhanced HIV viral suppression, reduced acquired ART resistance and improved clinical outcomes in low- and middle-income countries (LMICs) (8,9). When administered as a once-daily fixed dose combination, INSTI-based ART regimens have better tolerability, adherence, efficacy, and durability with a lower incidence of adverse events compared to older ART regimens (10-12). Due to these positive characteristics and flexibility, INSTI-based ART regimens have been proposed as a 'universal ART' for widespread use, including in patients with MDR-TB HIV co-infection [13,14].

Differentiated service delivery (DSD) is an innovative patient-centered care model, developed for people living with HIV, tailored to their health status and clinical needs, and informed by social, behavioral, and structural factors. DSD is an approach to delivering HIV care and treatment that takes into account the diverse needs and preferences of people living with HIV, and seeks to provide high-quality care responsive to those needs (15-17). DSD modalities may include mHealth, psychosocial support, adherence support groups, and community-based care. In South Africa, our team has piloted mHealth-guided adherence support using electronic dose monitoring, adherence support groups, and individual counseling using a motivational-interviewing approach for patients co-infected with MDR-TB and HIV (17 - 19).

Rationale for a Differentiate Service Delivery Titrated Intervention to Enhance Medication Adherence and Improve a Composite Treatment Outcome in MDR-TB HIV Co-infection

To date, TB control programs have used directly observed therapy (DOT) as the centerpiece of treatment delivery and adherence support (20), and a DSD approach has not been adapted for the DR-TB HIV care cascade. We propose extending the DSD framework to MDR-TB HIV to enhance medication adherence and retention in care to improve clinical and biological outcomes. We will implement an innovative, adaptive adherence intervention targeting reduction of barriers and enhancement of facilitators. Consistent with a DSD framework, this adaptive, randomized trial will deliver differentiated levels of service within each intervention arm depending on participants needs, with a focus on supporting patients facing more severe adherence challenges.

Building on this foundational work, we have designed an adaptive randomized controlled trial to evaluate the effect of different modes of treatment adherence support, titrated in intensity using a DSD framework, in South African patients with MDR-TB and HIV treated with bedaquiline-containing TB regimens and ART (primarily INSTI-based), on a primary composite outcome of MDR-TB and HIV treatment success.

Methods

Clinical trial objectives

The primary objective of this trial is to compare the effect of adherence support interventions on clinical and biological endpoints using an adaptive randomized platform. We hypothesized that in a randomized, adaptive implementation trial, the psychosocial + mHealth support arm will be associated with improvement in a composite MDR-TB and HIV clinical outcome compared to mHealth, psychosocial support, or enhanced standard of care arms.

The primary outcome will be a comparison of the percentage of participants achieving a composite of undetectable HIV viral load, TB culture conversion, survival, and retention in care at 12 months in each arm. Secondary outcomes will include all components of the primary outcome (all-cause mortality, MTB culture conversion, loss to follow up, HIV viral load) as well as a quantitative evaluation of adherence on TB and HIV treatment response (**Textbox 1**).

Trial design

This study will follow a four-arm adaptive trial design to evaluate four adherence support strategies on a combined endpoint in adults with confirmed MDR-TB and HIV initiating bedaquiline-containing MDR-TB treatment regimens and on ART in KwaZulu-Natal, South Africa (**Figure 1**). Interventions arms include **Arm 1** enhanced standard of care; **Arm 2** psychosocial support; **Arm 3** mHealth using cellular-enabled electronic dose monitoring; **Arm 4** combined mHealth and psychosocial support (**Textbox 2**). The level of support will be titrated using a differentiated service delivery (DSD)-informed assessment of treatment support needs.

Trial population and setting

Eligible participants will be consecutively recruited adult patients (age ≥ 18 years) meeting all of the following inclusion criteria; (1) culture or molecular test positive for TB, (2) molecular test positive for HIV or with a known or documented history of HIV, (3) drug-susceptibility testing by molecular (i.e. GeneXpert MTB/RIF) or conventional testing demonstrating at least rifampicin-resistant TB, (4) initiating treatment with a bedaquiline-containing TB regimen within 4 weeks of enrollment and with no prior bedaquiline exposure, (5) on treatment with ART regimen, including dolutegravir-containing combination ART regimen, or starting ART within 4 weeks of enrollment, (6) capacity for informed consent in either isiZulu or English. Patients will be excluded from the study if they do not meet eligibility criteria, are prisoners, are pregnant at time of enrollment, or are considered by study team to be too ill to participate in the trial.

Participants will be recruited from MDR-TB treatment facilities and affiliated outpatient TB clinics in Durban, South Africa. Study visits will be conducted within the established research infrastructure at the Durban CAPRISA Springfield Clinical Research Site.

Adaptive randomization

Eligible participants will be assigned to one of four intervention arms at baseline using a two-step randomization. Participants will be initially randomized to Arm 1 vs Arms 2-4 in a 1:3 ratio, using a minimization method to achieve balance over baseline variables (undetectable vs detectable HIV viral load, 6-month vs. extended MDR-TB regimen, inpatient vs outpatient). Bayesian adaptation will be accomplished by utilizing a run-in period where the first 40 participants will be randomized without any adaptation. After the first 40 participants have been randomized and achieve preliminary outcomes at 4 months, results will be incorporated in a Bayesian fashion to modify the randomization procedure for subsequent participants weighting randomization toward favorable study arms. A web-based application (R shiny 1.7.4) will be used to perform adaptive randomization in real-time.

Trial interventions

After assignment into one of 4 arms as described above each participant will receive an Arm specific intervention (**Textbox 2**).

Enhanced standard of care (*Arm 1*) will include usual care as administered by hospital and clinic staff, enhanced by study staff providing treatment literacy and extra training for treating physicians, nurses, pharmacists, and social workers prior to trial initiation and periodically with refresher trainings throughout the trial duration.

The psychosocial support intervention (*Arm 2*) will include discharge or community treatment planning depending on inpatient vs. outpatient treatment status, monthly individual counselling, community adherence support groups, and home visits. The intensity of the support will be calibrated based on monthly assessment by study counsellors. Participants will be administered standardized TB and ART adherence assessment questionnaires monthly. Participants with a low standardized adherence score will be considered at risk for non-adherence and will have the intensity of the intervention increased and may include: telephonic check-ins by study staff, increased frequency of counselling sessions from monthly to biweekly, and may have a home visit conducted by a multidisciplinary study team. Monthly adherence support groups will not be calibrated.

Participants randomized into the mHealth intervention (*Arm 3*) will receive two Wisepill RT3000 cellular-enabled electronic pill boxes ('Wisepill'): one with ART and one with bedaquiline. They will also receive training on pill box loading, charging, and storage. Each Wisepill device will be appropriately marked to avoid confusion and stigma. Pill box openings will serve as a surrogate for adherence to ART and bedaquiline, respectively. Each participant will select a text message reminder from a guided menu of choices. Participants will receive a weekly text message encouraging regular adherence. For bedaquiline, one missed, and for ART, 2 missed EDM openings within a two-week window (not due to technical issues) will trigger an additional text message reminding the patient to take their medication. For EDM openings recorded outside the EDM dose window or continued missed doses, it will be up to the investigators' discretion to issue additional text messages or semi-scripted study calls to support adherence. The psychosocial support + mHealth intervention (*Arm 4*) will include a combination of Arms 2 and 3. Patients will be considered at risk for non-adherence by a low adherence score as described in Arm 2

and/or missed openings recorded by Wisepill devices as described in Arm 3 and increased support will be delivered as described above.

Trial timeline

The trial timeline will include 6 months to train study staff on the protocol, including the randomization strategy and software use. Approximately four years will be allowed for enrollment. Participants will be followed monthly through the 6 months of intervention with an additional in-person visit at 12 months to establish the primary outcome, and through the end of treatment (approximately 18 months after treatment initiation) telephonically. Data for the study will be collected at the following visits: a) baseline (enrollment) visit, b) monthly clinical visits (months 1-6), c) follow-up or end of treatment visit, and d) at community adherence support groups (**Figure 2**). Sputum will be collected monthly, and serum for HIV viral load testing will be collected at months 0, 2, 6, 12.

Informed consent

A member of the study staff will explain the protocol and informed consent documents, with opportunity to ask questions, prior to seeking informed consent in the preferred language of the potential participant (English or isiZulu).

Statistical analysis

The study is powered to enroll a total of 360 participants, who will be randomly assigned to one of four trial arms (**Textbox 2**). A Bayesian adaptive randomization algorithm will be used to assign interventions to participants to improve the power of detecting any superior arm(s) and to increase the number of participants treated in the better arm(s) during the study. We varied the estimated success rate, based on prior observational data in the same population, between 70% - 90% with power as low as 74% and as high as 98% depending on differences in success rates (**Table 1**). Family-wise error rate, the probability of erroneously declaring *any* non-superior arm(s) superior, will be between 0.005 and 0.020 depending on treatment success in the various arms.

Data management

Prior to enrollment, all research staff will participate in Human Subjects Protection training/Good Clinical Practice training to ensure sensitive data confidentiality. Informed Consent Forms and all forms containing patient identifiers will be kept separate from study forms in a secure, locked location. Upon enrollment, participants will be assigned a unique study identifier (PID) assigned by the CAPRISA Data Management Center, which will be used on all case record forms (CRFs) to identify the participant for the duration of the study. 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 designated members of the study staff will have access to the key linking the study PID data to patient identifiers.

Data safety monitoring and review

Quality checks will be performed on the data entered into the RedCap database and completed CRFs will be checked by the quality control officers. CAPRISA data managers will verify and validate patient data and ensure Quality Control reports are produced and approved per CAPRISA data management Standard Operating Procedures (SOPs). The CAPRISA laboratory manager will ensure that all involved laboratories are compliant with Good Laboratory Practice. The CAPRISA pharmacist will provide oversight for the preparation of the electronic pillboxes and pill counts. Quality assurance/Quality control of data will be undertaken according to established CAPRISA SOPs.

Community involvement

Engagement with the provincial department of health and local health personnel has been initiated. Community engagement through the CAPRISA community programme and a study community advisory board (CAB) is ongoing.

Ethics and dissemination

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/Good Clinical Practice. The trial protocol have received approval from the IRB at Columbia University and University of KwaZulu-Natal (UKZN) Biomedical Research Ethics Committee (BREC).

Discussion

Summary

Each year, approximately 14,000 people are diagnosed with MDR-TB and HIV in South Africa (1). Medication adherence is a key predictor of TB and HIV treatment outcomes and emergent resistance to both ART and TB medications, and dual adherence to TB medications and ART remains severely understudied in high burden TB/HIV settings (21-23). This trial sited in Durban South Africa, global epicenter of the MDR-TB HIV syndemic, will allow us to evaluate the individual and combined contributions of mHealth and psychosocial support in the treatment of MDR-TB in people living with HIV. Using a DSD framework, we will characterize the intensity of support required to promote adherence to TB medication within each trial arm. In addition, this trial will inform optimal management of MDR-TB and HIV using cutting-edge TB and HIV treatment regimens in an operational public health system in a high burden LMIC setting.

Limitations

Actual and potential limitations to this trial include potential challenges to feasible implementation in a low burden setting, lack of generalizability, potential for insufficient adherence support, and potential lack of power. The Wisepill RT3000 device is costly (~US \$100/device) which may be cost prohibitive in LMICs. However, devices may be re-used, less costly EDMs are available, and the cost of MDR-TB treatment failure is high and cascades when the cost associated with community transmission is included. We anticipate following this trial, if successful, with a cost-effectiveness analysis and potentially a larger more operational trial using a less expensive EDM. The MDR-TB HIV co-infection syndemic in KwaZulu-Natal, South Africa is unique in its intensity as well as cultural and health systems factors. These results while immediately generalizable to similar southern African settings may not be entirely generalizable to MDR-TB treatment in Southeast Asia for example. There is a concern that the intervention arms may not be sufficiently impactful to change deep-seated behaviour ('underdosed') since adherence challenged patients may have substantial, refractory behavioural or structural challenges to adherence. While this may be accurate, a more intensive interventional approach was felt to be not feasible since it may not be implementable in routine programmatic settings. Although we consider our trial adequately powered based on assumptions derived from previous data, if the interventions perform similarly or rates of overall success are higher than expected the trial may be unpowered to demonstrate a true difference between intervention arms.

Conclusion

We anticipate this randomized, adaptive trial design to be a highly efficient and ethical approach to evaluating the comparative effectiveness of mHealth and psychosocial support to improve MDR-TB HIV co-infection outcomes. Further this trial will extend a DSD framework, previously developed to support HIV treatment and primarily focused on patients who are stable on ART, to patients who are co-infected with MDR-TB and HIV, including those who struggle with medication adherence. This trial takes advantage of our team's depth of experience with this population and substantial pilot evidence to design and implement an intervention. We also use the opportunity of the roll out of bedaquiline-based all-oral short course regimens for MDR-TB treatment and the availability of INSTI-based fixed dose combination ART in the South African public health system to study operational issues around MDR-TB/HIV treatment. Finally, we are in close communication with the South African public health system as we implement this trial including provincial and national laboratories and public health bodies.

Declarations

Trial Status

Protocol Version 3.0 | 2FEB2023

Start of recruitment: March 06, 2023

Approximate completion of recruitment: March 01, 2027

Trial Registration

ClinicalTrials.gov: NCT05633056

Date of trial registration: December 1st, 2022

Ethics approval and consent to participate

The protocol and supporting documents were submitted concurrently and have received approval from the HRPO IRB at Columbia University and Biomedical Research Ethics Committee (BREC). Written informed consent will be obtained from all participants.

Consent for publication

Not applicable

Availability of data and materials

Only the South Africa 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.

Competing interests

The authors declare that they have no competing interests.

Funding

Funded by The National Institutes of Health (NIH). Grant # R01 AI167798-01A1

Author's contributions

Conceptualization of study: MO, JZ, AD

Design of study: MO, JZ, RP, AD

Developing the protocol: MO, JZ, RP, AW

Substantive changes to the protocol: MO, JZ, JR, RP

Drafting the manuscript: MO, JZ, JR, RP, KG

All authors were involved in editing the final manuscript.

Acknowledgements

Not applicable

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Table 1

Table 1. Adaptive study design power analysis showing two possible effect estimates, and various scenarios

Scenario	Success rate (%)				Power*	FWER**
	Standard	mHealth	Socio-behavioral	mHealth + Socio-behavioral		
Null	70%	70%	70%	70%	--	0.019
Single	70%	70%	70%	90%	0.95	0.010
Two	70%	70%	90%	90%	0.97	0.006
All	70%	90%	90%	90%	0.98	---
Additive	70%	80%	80%	90%	0.92	---
<hr/>						
Null	75%	75%	75%	75%	--	0.020
Single	75%	75%	75%	90%	0.77	0.009
Two	75%	75%	90%	90%	0.84	0.005
All	75%	90%	90%	90%	0.87	---
Additive	75%	80%	83%	90%	0.74	---

*Power = Probability of correctly identifying at least one superior arm compared to standard

**FWER = Family-wise error rate, the probability of erroneously declaring *any* non-superior arm(s) superior

Textbox 1 and 2

Textbox 1 and 2 are available in Supplementary Files section.

Figures

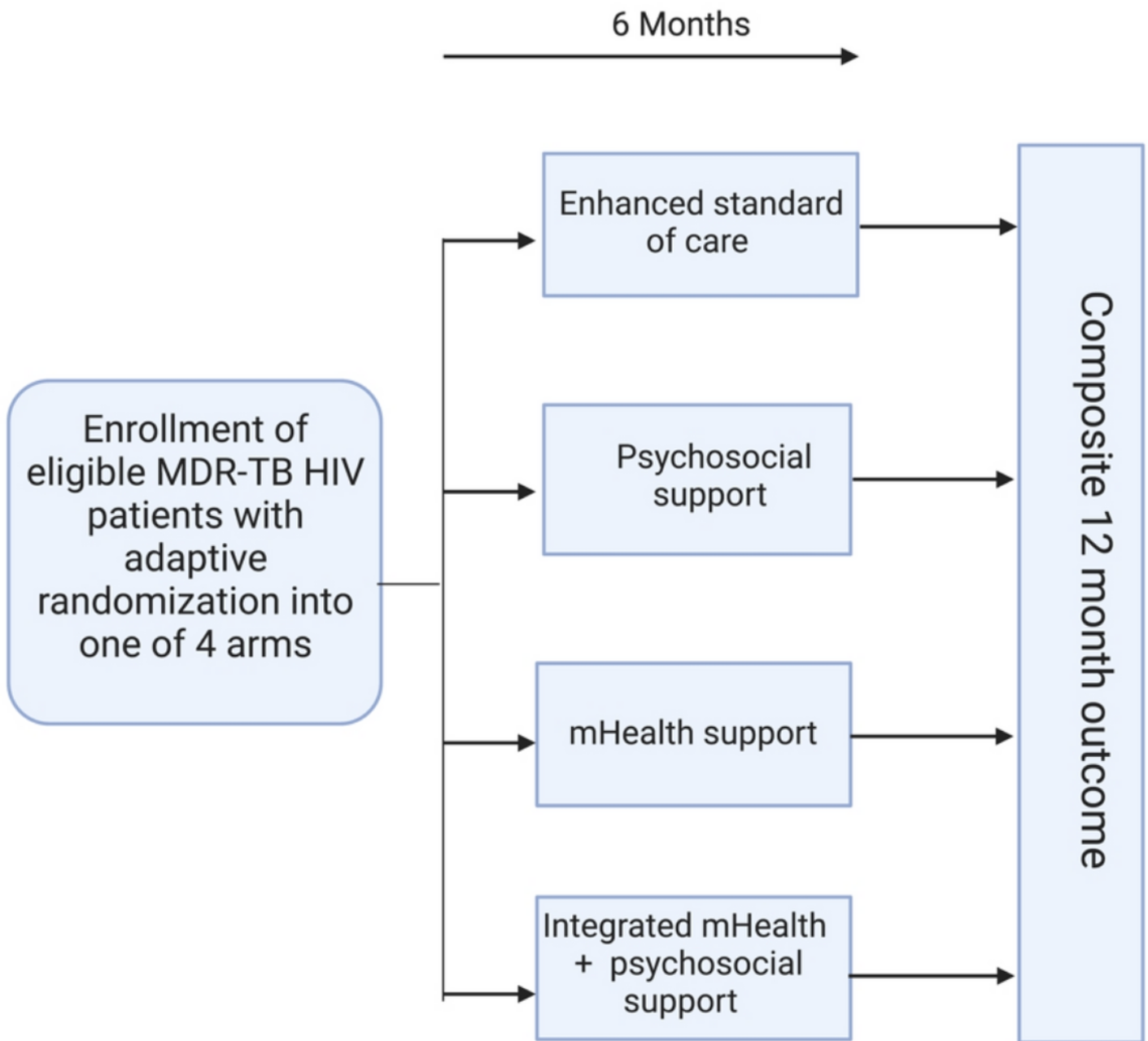


Figure 1

Study design overview

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 counselling	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	x	x
Blood Sample collection for storage	x		x				x		
Depression Screen	x						x	x	
Stigma Screen	x						x	x	
sIMB Questionnaire	x			x			x	x	
Post Trial call									X
Intervention groups only									
Arm 2									
TB adherence assessment (WAS)		x	x	x	x	x	x	x*	
Monthly counseling intervention (MCI) ²		x	x	x	x	x	x		
Adherence Support Groups (ASG)		x	x	x	x	x	x		
Home visits ⁴	As needed basis								
Post hospital 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) triggered by non-adherence as detected by Wisepill non-opening.								
Arm 4									
	Will include all available interventional tools**								
Optional Sub-study In-Depth Interviews (IDI) ⁴		x				x			

*Monthly pharmacy records will be obtained; Routine HIV viral loads, sputum culture results will be collected from the clinic

*If participant remains on treatment

²Frequency may increase based on need

³Participant 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.

⁴A sub-set of participants from each arm will be selected to participate in an IDI. Participant may opt-out. Two interviews should occur, one between months 2-3 and the second between months 6-9.

Figure 2

Schedule of Study Evaluations

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TextBox1and2.docx](#)
- [ADAPTIVProtocolversion3.0draftwtc.docx](#)
- [SPIRITChecklistFinal.docx](#)