Measuring adherence using digital adherence technologies (DATs) in the new BPAL Regimen to determine influence on microbiological outcomes and Bedaquiline resistance [DRTB-MATE]

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DRTB in South Africa

- Drug resistant TB (DR-TB) continues to be a public health threat in South Africa having contributed 11000 (3.9%) new TB cases in 2022
- Despite the policy change introducing a shorter MDR/RR-TB regimen, adherence to MDR/RR-TB treatment is still a challenge in South Africa. In 2022, South Africa's MDR/RR-TB treatment success rate was 79%
- Factors associated with non-adherence to DR-TB treatment include the long duration of treatment, high medication burden, frequent side effects, socio-economic factors, substance use, and mental health issues
- New drugs such as **bedaquiline** (WHO Class A) and delamanid (WHO Class C), are the mainstay of new regimens for DR-TB and the long half life of bedaquiline is particularly worrying for emergence of drug resistance.

Bedaquiline Resistance

- In South Africa, bedaquiline resistance has already been described in samples from 2015 – 2019, in as many as 3.8% of patients starting bedaquiline containing regimens. These were associated with previous exposure to bedaquiline or clofazimine (Odds Ratio 7.1 [95% CI 2.3 – 21.9]).
- *Rv0678* mutations were the sole genetic basis of phenotypic resistance.
- Resistance during treatment developed in 16 (2.3%) of 695 patients, at a median of 90 days (IQR 62–195).

Ismael, Lancet Infectious Disease 2022

Evidence so far on digital adherence technologies

- Evidence for digital adherence tools is mixed: improved adherence – from 1ST China trial, TB MATE, ASCENT
- No improvement in treatment outcomes overall – 2nd China trial, TB MATE, ASCENT
- Very little information from DRTB but the use of this technologies may be important in showing relationship between treatment outcomes.

Liu, Plos Medicine 2015

Liu, Lancet Global Health 2023

Effectiveness of MERM in DR-TB

Bedaquiline Adherence Measured by Electronic Dose Monitoring Predicts Clinical Outcomes in the Treatment of Patients With Multidrug-Resistant Tuberculosis and HIV/AIDS

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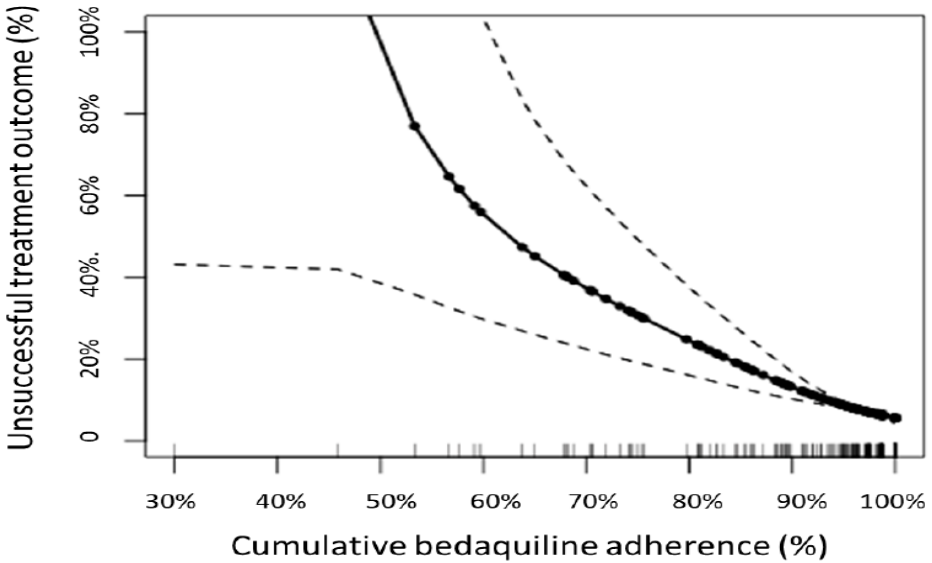
Figure S1. Cubic spline demonstrating the relationship between bedaquiline adherence and outcome



Study Aim

To determine whether adherence impacts microbiological outcomes in persons with DR-TB receiving BPAL,

and whether an adherence package (including psychosocial assessment, medication monitors and a differentiated care approach) impacts these outcomes and ultimately Bedaquiline resistance acquisition

Study Objectives

Primary Objectives

- To **determine the association between adherence and microbiological treatment outcomes and relapse** (culture conversion at 2M, time to culture conversion and treatment failure and relapse within 18M post-treatment start)
- To **determine the association between adherence and acquisition of BDQ resistance** (during treatment & in the 12-month follow-up period)
- To **determine genotypic and phenotypic drug resistance levels at treatment initiation, end of treatment** and with failure during treatment or relapse in the 12 month follow-up period.

Secondary Objectives:

- To **compare microbiological outcomes** (culture conversion at 2M, time to culture conversion, treatment failure, recurrence within 18M) amongst those who show high fidelity to the monitor compared those who do not use the monitor or have low fidelity to use.
- To **assess the feasibility of the psychosocial assessment and support**
- To **model the impact of improved adherence on mortality, TB incidence and incidence of BDQ resistance** in SA

Study population

We plan to implement the study in the fewest number of sites feasible to enable us to complete recruitment within 12-18 months.

We plan to recruit 1200 participants for the primary cohort over a 12-18 month period (see sample size estimate for the rationale).

- Clinics: > 15 RR-TB patients treated in previous year
- Children above 15 years of age and non-pregnant adults with RR-TB
- On BPAL-L or BPAL (if fluoroquinolone resistant) regimen
- Participants with and without HIV
- Started RR-TB treatment within 4 weeks of enrolment
- Both those with and without previous BDQ exposure
- Informed consent provided
- Expecting to be in the region in the next year

Challenges of the trial

- De-centralised care – enrolments will be across a lot of clinics
- Large number of DRTB patients to recruit over short period of time
- Number of trials already recruiting
- Solution
  - Partnered and embedding study in another trial

Laboratory testing to be done

- Bedaquiline resistance testing
- Whole genome testing
- Drug level testing

THANK YOU