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# Individualised management of MDR and XDR-TB in South Africa using Whole Genome Sequencing (CAPRISA 020-INDEX Study)

**RESIST TB Webinar**

**29 July 2020**


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Scientist: CAPRISA HIV-TB Treatment Research Programme



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# Overview

- Whole Genome Sequencing (WGS) for management of Drug-Resistant TB (DR-TB)
- INDEX Study Design
- Intervention with Case Study
- Implementation Challenges
- Further Research
- Summary

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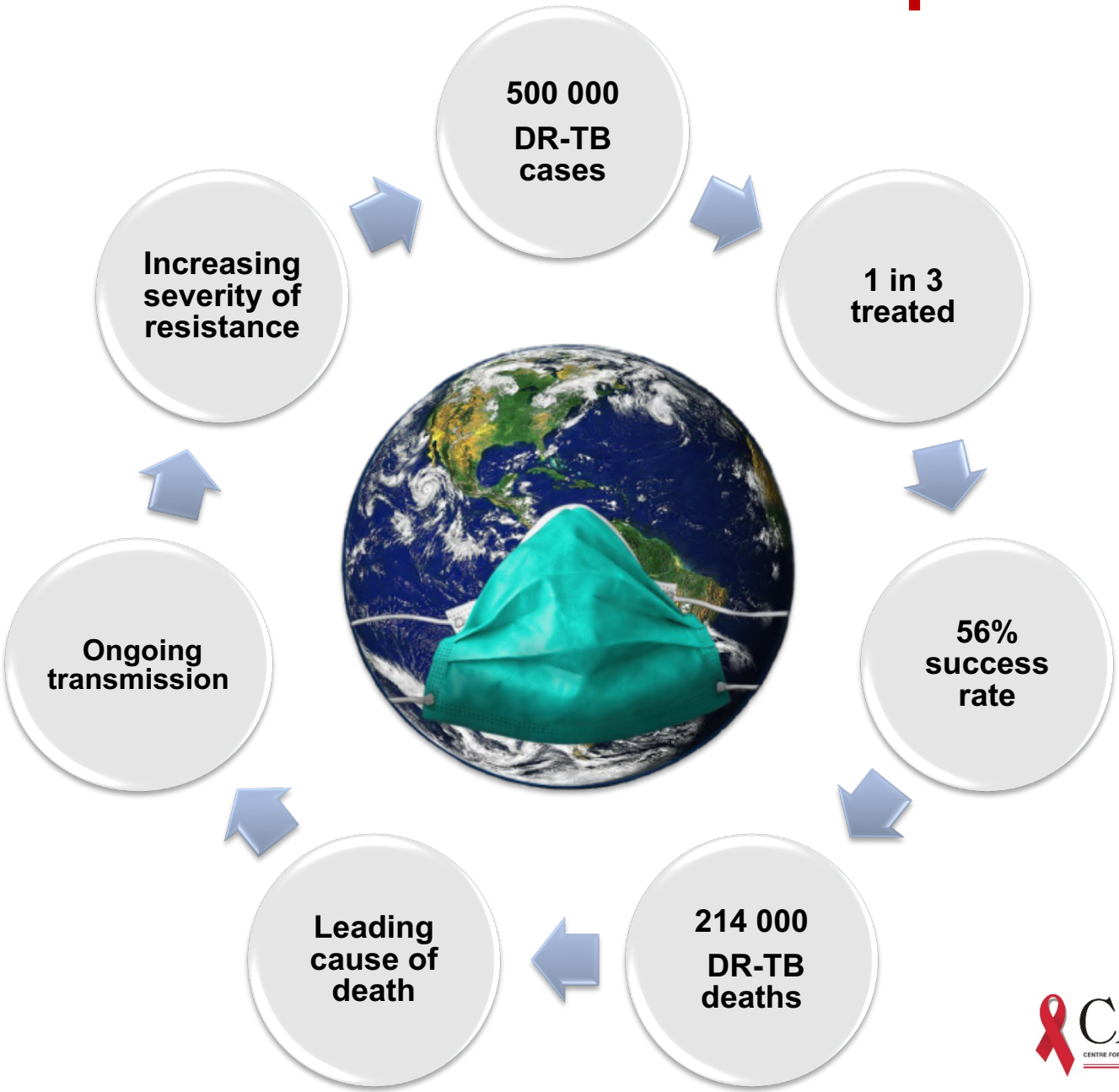
# The Scale of the DR-TB Epidemic

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# WGS for personalized management of DR-TB

- **New diagnostic and treatment approaches urgently warranted:**
  - Delayed detection & incomplete resistance characterisation
  - Current culture-based & molecular diagnostic tools - mis-diagnosis, inappropriate treatment initiation and amplification of drug resistance
- **To overcome these challenges – TB programs use standardized regimens**
- **Personalized management through WGS: a compelling alternative to conventional methods**

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# Rationale

- **Paradigm shift**
  - From standard DR-TB regimen
  - To a personalised medicine approach
- **WGS individualised treatment:**
  - Demonstrated in high-income, low TB burden settings
  - Impact on outcomes: unknown
- **INDEX Study: RCT in high-burden setting with increased prevalence of HIV co-infection and second-line drug resistance**

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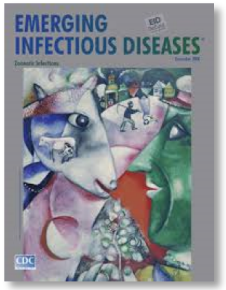
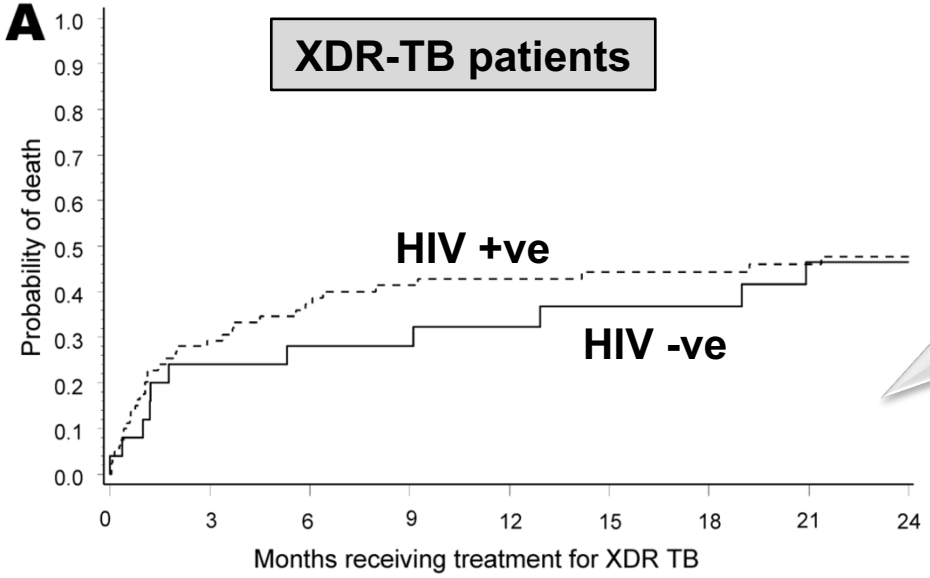
# DR-TB in South Africa

- South Africa has among the highest DR-TB incidence globally
- Accounts for 20% of all DR-TB cases in Africa
- KwaZulu-Natal Province – 50% of the national DR-TB cases




## Treatment Outcomes for Extensively Drug-Resistant Tuberculosis and HIV Co-infection

Max R. O'Donnell, Nesri Padayatchi, Charlotte Kvasnovsky, Lise Werner, Iqbal Master, and C. Robert Horsburgh, Jr.




**XDR-TB OUTCOMES POOR**
24 month outcomes (%):

- Cure & Completed: 22
- Default: 16.7
- Failure: 19.3
- Died: 42

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# The Individualized M(X) Drug-resistant TB Treatment Strategy Study (INDEX)

| | |
|---|---|
| **Primary Objective** | To determine if a WGS-derived individualized treatment approach in patients with drug-resistant TB will improve culture negative survival rates at 6 months post treatment initiation |
| **Design** | Randomized Controlled Trial |
| **Hypothesis** | Treatment success is one third higher with a WGS-derived individualized treatment approach |
| **Duration** | 18 to 24 months |
| **Population** | Patients ≥ 18 years with pulmonary TB and at least RIF resistance |
| **Sample Size** | 448 |
| **Primary Endpoint** | Culture negative survival rates at 6 months post treatment initiation |

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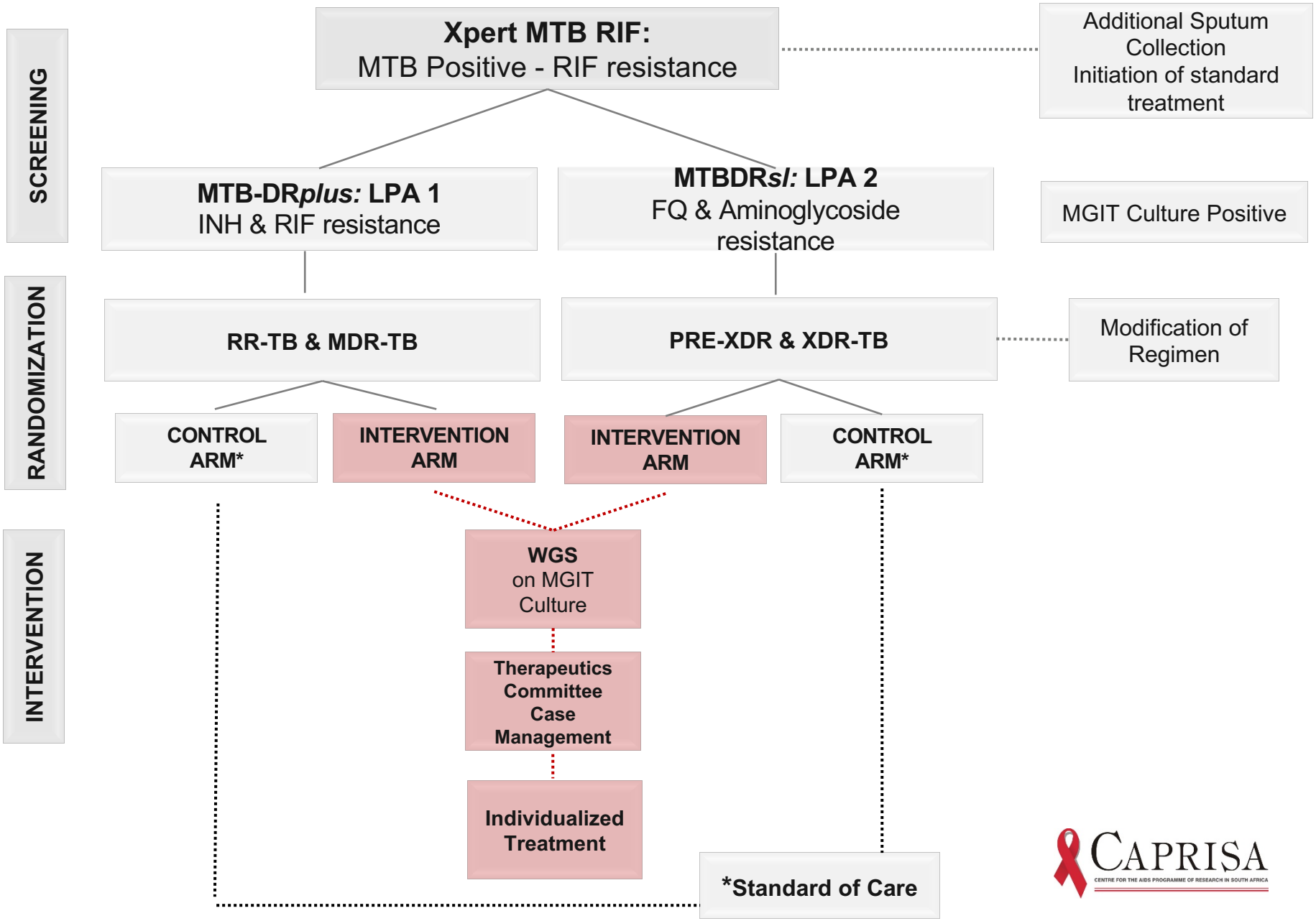
# Study Approach

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INTERVENTION

**WGS**
from MGIT Culture

**Therapeutics Committee Case Management**

**Individualized Treatment**

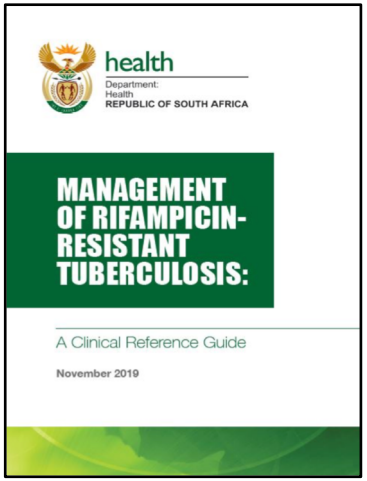
## Analysis of WGS results using published literature and databases:

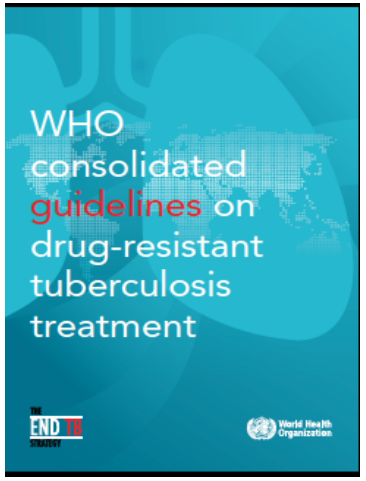
- Prevalence in clinical isolates and association with phenotypic susceptibility
- Grade mutations to direct inclusion or exclusion of drugs in regimen:
  - **High Confidence:** – **Drug Excluded from regimen:** Frequent mutations with high a correlation between phenotypic and genotypic testing platforms. Allelic exchange/supporting data demonstrating association of mutation
  - **Intermediate Confidence: Drug included in absence of available alternate drugs for an effective regimen.** Mutations occurring at lower frequencies only detected in resistant isolate
  - **Low Confidence: Drug is included in regimen.** No association with resistance – mutations represent lineage markers or compensatory/fitness change

## Selecting a personalized regimen:

- Therapeutics review committee comprising local and international DR-TB experts including scientists, facility-based DR-TB clinicians and a microbiologist
- Face-to-face or virtual team discussion using patients clinical and laboratory information together with WGS analysis
- Current regimen reviewed for adequacy

- New regimen proposed using principles outlined by South African National Department of Health & WHO
- At least two members must be in agreement with analysis and recommendations to effect regimen change



# Case Presentation

- **41 year old male presented at the specialist DR-TB referral hospital on 7th March 2019**
- **2 week history of cough, night sweats, chest pain, weight loss & poor appetite**
- **Previous episode of TB in 2004 – cured**
- **HIV co-infected on ART since 2004: tenofovir/lamivudine/efavirenz**

**MTB PROFILING:**

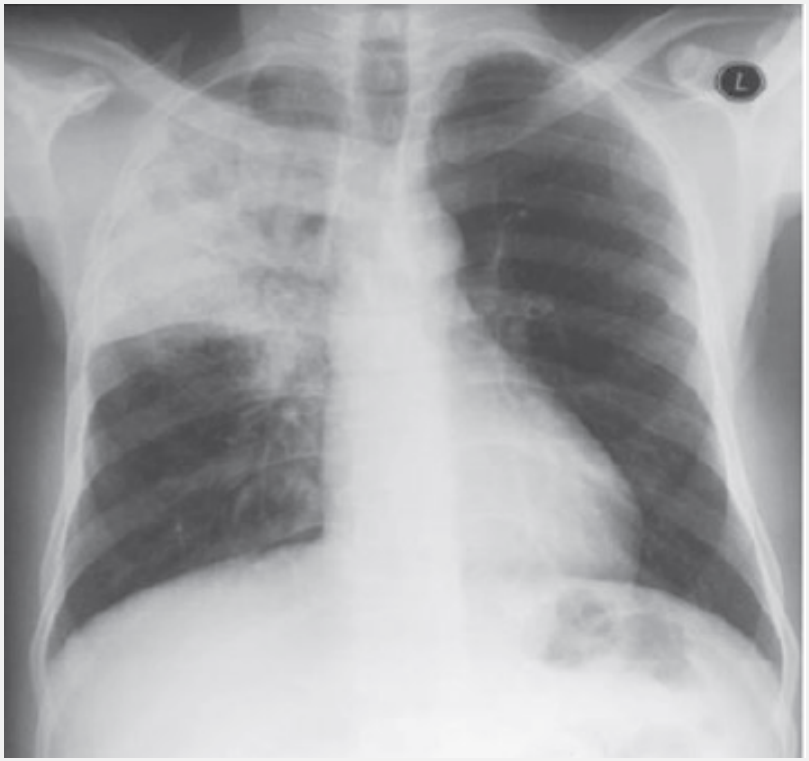
**Xpert MTB RIF/Ultra:**
MTB Positive + RIF Resistance

**LPA 1:**
INH & RIF resistance

**LPA 2:**
Uninterpretable

**Sputum Microscopy:** Scanty Positive (7AFB/100 immersion fields)

**MGIT Culture:** Positive (13 days)



**BASELINE CHEST RADIOGRAPH:**
**Extensive disease with consolidation of the right upper & middle lobes**
**07 March 2019**

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# Patient Management

**INITIAL TREATMENT REGIMEN: 9 month short-course**

- BEDAQUILINE: 200mg 3X week (400mg for 2 weeks initially)
- Daily:
- LINEZOLID 600mg
- HIGH-DOSE ISONIAZID 900mg
- LEVOFLOXACIN: 1g
- CLOFAZAMINE: 100mg
- PYRAZINAMIDE: 1.25g
- ETHAMBUTOL: 1.2g

**ART REGIMEN SWITCH:**

Interaction between Bedaquiline and Efavirenz:
Tenofovir/emtricibine/nevirapine

**DISCONTINUATION OF LINEZOLID:**

1 month following treatment initiation due to anaemia
~25% decrease in haemoglobin level

| Date | 05 Mar 19 | 14 Mar 19 | 28 Mar 19 | 11 Apr 19 | 24Apr 19 |
|---|---|---|---|---|---|
| Hb (g/dl) | 11.4 | 12.0 | 10.3 | 8.9 | 9.7 |
| eGFR | 58 | >60 | >60 | >60 | - |

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# WGS Results

**Whole Genome Sequencing of M. tuberculosis**

Genome Coverage 43

| Drug | Gene | Nucleotide Change | Amino Acid Change | Frequency |
|---|---|---|---|---|
| Isoniazid inhA Promoter (mabA) | | c-15t | | 100 % |
| Isoniazid | inhA | t581c | Ile194Thr | 100 % |
| Rifampicin | rpoB | c1349t | Ser450Leu | 100 % |
| Ethambutol | embB | a916g | Met306Val | 100 % |
| Pyrazinamide | pncA | c22t | Asp8Asn | 100 % |
| Ethionamide | inhA | t581c | Ile194Thr | 100 % |

The mutations in rpoB, inhA promoter, embB, inhA and pncA are known resistance determinants. The mutation detected in the inhA promoter has been associated with cross-resistance to ethionamide.

**WGS conducted by the National Institute of Communicable Diseases: Centre for Tuberculosis: MiSeq; Illumina V3.0 and bioinformatics analysis using the CLC Genomics Workbench v6.0.1**

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# WGS Analysis

| Drug Class | Drug | Call* | Description |
|---|---|---|---|
| Group One First Line | Isoniazid | R | ***inhA Promoter (mabA)*; c-15t - Results in low-level isoniazid resistance and ethionamide cross-resistance. High dose isoniazid can be included in the regimen. If co-occuring with a katG mutation, high-dose isoniazid resistance is assumed and thus, drug is excluded. Ethionamide excluded from regimen**<br><br>***inhA;* Ile194Thr (t581c)- Leung et al. 2005 described this mutation in 1 clinical isolate associated with an MIC of 1.0 mg/L. However, they conducted kinetic analysis to characterise the mutation. They found that is resulted in a decreased affainity for NADH-enzyme binding. Jagelski et al. 2015 subsequently reported the mutation in 2 inh mono-resistant isolates and 1 MDR isolate.** |
| | Rifampicin | R | ***rpoB;* Ser450Leu (c1349t) - Strong association with high-level resistance to RIF. Most common mutation associated with RIF R** |
| | Ethambutol | R | ***embB;* Met306Val (a916g) - High-level resistance to EMB. High frequency mutation associated with a four-fold increase in MIC.High indication for ethambutol resistance** |
| | Pyrazinamide | R | ***pncA;* Asp8Asn (c22t) – This mutation falls within the three 'hot-spot' regions of the pncA gene (codons 3-17; 61-85; 61-85). Only described in 1 isolate in systematic review of 2760 isolates, however, it ocuured as a double mutant *(Ramirez-Busby)*. Described as high-confidence by *Miotto et al.* as mutation that affect the catalytic residues and amino acids recruited in the scaffold of the active site or directly/indirectly involved in the coordination of the $Fe^{2+}$ ions thus high-confidence for resistance. (*Miotto* 2014)** |
| | Streptomycin | S | ***Wild Type*** |
| Group Two Second-Line Injectables | Aminoglycosides | S | ***Wild Type*** |
| Group Three | Fluoroquinolones | S | ***Wild Type*** |
| Group 4 | Ethionamide | R | ***InhA Promoter (mabA)*; c-15t – cross-resistance between INH and ethionamide** |
| | PAS | S | ***Wild Type*** |
| | Linezolid | S | ***Wild Type*** |
| | Bedaquiline | S | ***Wild Type*** |
| | Delamanid | S | ***Wild Type*** |

* Call: R=Resistance R (HC = High Confidence; IC = Intermediate Confidence; LC = Low Confidence) S = Susceptible

# DST Results

| *Phenotypic Drug Susceptibility Testing (MIGIT Culture Based)* | |
|---|---|
| Bedaquiline (1.0 mg/L) | Sensitive |
| Clofazimine (1.0 mg/L) | Sensitive |
| Isoniazid Low (0.1 mg/L) | Resistant |
| Isoniazid High (0.4 mg/L) | Resistant |
| Levofloxacin (1.0 mg/L) | Sensitive |
| Linezolid (1.0 mg/L) | Sensitive |
| Moxifloxacin Low (0.25 mg/L) | Sensitive |
| Moxifloxacin High (1.0 mg/L) | Sensitive |

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# Individualized Regimen & Outcome

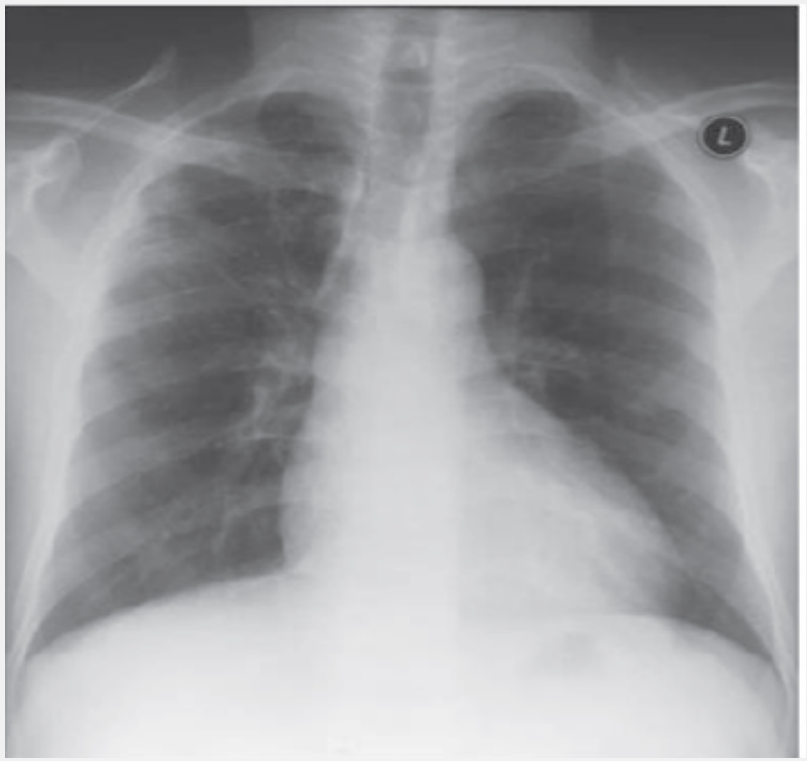
**FACTORS CONSIDERED BY THERAPEUTICS COMMITTEE:**

EXTENSIVE DISEASE: CHEST RADIOGRAPH
ADDITIONAL *inhA* MUTATION SUPPORTED BY DST RESULT
CONFIRMED PYRAZINAMIDE AND ETHAMBUTOL RESISTANCE

**DECISION :**
**INDIVIDUALIZED 18 MONTH REGIMEN:**
BEDAQUILINE: 200mg 3X week
LINEZOLID: re-challenge 600mg daily
LEVOFLOXACIN: 1g
CLOFAZAMINE: 100mg
TERIDIZONE: 750mg
} Daily

**CULTURE CONVERSION: MONTH 2**

**CURRENT STATUS: 15 months of treatment**



**END OF INTENSIVE PHASE-CHEST RADIOGRAPH:**
**Resolution of Disease**
**29 August 2019**

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# Case Highlights

- **Role of WGS when used with extended phenotypic DST in clinical case management:**
  - Intensive phase contained 3 effective drugs only: bedaquiline, levofloxacin and clofazimine,
  - further reduction in number of effective drugs in continuation phase: levofloxacin and clofazimine
  - Could have led to amplification of resistance to key drugs and sub-optimal treatment outcomes
- **WGS: Identification of additional *inhA* mutation, ethambutol and pyrazinamide resistance**
  - Conventional tests lack these markers despite high background burden of resistance to these drugs
  - Inadequacy of commonly selected companion drugs
- **Phenotypic resistance testing remains valuable:**
  - New drugs and disputes with genotypic correlation of mutations

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# Implementation Challenges

- **Individualized data-driven treatment provision challenging:**
  - Lengthy turn-around time for culture-based WGS - lack of assays for direct sequencing from sputum
  - Limited curated data on genotypic-phenotypic correlations available - comprehensive per patient review required
  - Need for phenotypic testing: new drugs and disputed mutations
  - Limited drug choices available for DR-TB
  - Limited utility of the genome sequence - era of short-course standardized regimens utilizing new drugs
  - Overlapping drug toxicities important factor in treatment choice
  - Numerous changes to treatment guidelines over the course of the study

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# Further Research

1. **Optimizing the clinical utility of WGS**
   - Direct sequencing from sputum using the Deeplex-MycTB assay - targeted genotypic 15 drug panel
   - Comprehensive phenotypic analysis
2. **Evolving drug-resistance**
   - Sequencing of serial samples to understand the development of resistance and clinical significance of heteroresistance
3. **Role of high-dose INH in DR-TB treatment**
   - Phenotypic analysis to understand the role of *katG* and *mabA* mutations
   - Time-kill experiments

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# Summary

- Current diagnostic platforms do not effectively guide DR-TB regimen selection
- Diagnostic adjuncts such as WGS and DST offer an innovative solution to overcoming these complexities
- Standardized approach to DR-TB treatment potentially unsustainable as drugs are lost faster than they can replaced
- The INDEX study approach may offer potential strategy for the use of WGS for personalized management of DR-TB

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# Acknowledgements


- **INDEX Study Participants**
- **INDEX Study Team**

  Prof Nesri Padayatchi (PI)
  Prof Kogie Naidoo (Co-PI)
  Dr Surie Chinappa
  Avika Haridutt
  Patience Mbatha
  Zanele Msimango
  Radha Narismmulu
  Lorelle Pillay

- **NICD-Centre for Tuberculosis**

  Dr Nazir Ismail
  Dr Shaheed Valley Omar
  Dr Farzana Ismail

- **Funders**

  CAPRISA
  EDCTP
  National Research Foundation of South Africa

- **INDEX Therapeutics Committee**

  Dr Sunita Chotoo (King DinuZulu Hospital, KZN, South Africa)
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