Principles of Management of Drug Resistant (DR) TB in adults

Advanced Clinical Care Program - Advanced TB and HIV Workshop
Amajuba District
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Presentation Outline

• Definitions of drug resistant (DR) TB
• Diagnosis of DR-TB
• Baseline Investigations and monitoring of patients
• Drug Side Effects
• Managing HIV/DR-TB Co-infected patients
• MDR-TB Outcome definitions
• Bedaquiline Program in KZN
• Case and questions
# DR-TB definitions

<table>
<thead>
<tr>
<th>Type of DR-TB</th>
<th>Definition</th>
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<tbody>
<tr>
<td>RR-TB</td>
<td>Resistance to Rifampicin with or without resistance to other TB medicines</td>
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<tr>
<td>INH Mono-resistant TB</td>
<td>Resistance to INH only</td>
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<tr>
<td>Poly-drug Resistant TB</td>
<td>Resistance to two or more anti-TB drugs other than Rifampicin (R) and Isoniazid (INH)</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Resistance to Rifampicin and INH, with or without resistance to other first line anti-TB drugs</td>
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<tr>
<td>Pre- XDR TB</td>
<td>Resistance to either any Fluoroquinolone OR to a second line Injectable drug in addition to MDR-TB</td>
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<tr>
<td>XDR-TB</td>
<td>Resistance to either any Fluoroquinolone AND to at least one of the second line Injectable drugs (CM,KM,AM) in addition to MDR-TB</td>
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MDR-TB
Resistance to Rifampicin and INH, with or without resistance to other first line anti-TB drugs

• Why is the definition of MDR TB based on resistance to these 2 drugs?

• They are the most important (potent) first line drugs to treat TB
Symptoms of DR- TB

• Same symptoms as Drug Sensitive TB

• Thus the diagnosis of DR TB is microbiologic
Molecular Testing

PCR – need confirmation with full sensitivity

Line Probe Assay (LPA) HAIN Test
- Rapid screening test for INH and Rif resistance
- Results in days

Gene Expert
- Point of care test- Result in hours
- Done directly on sputum- more sensitive than smear with higher yield
- Screens for TB
- Screens for Rif resistance only
## Interpreting LPA Results

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Meaning and Resistance Caused</th>
<th>Drugs you can use</th>
</tr>
</thead>
<tbody>
<tr>
<td>InhA</td>
<td>low level INH resistance and confers resistance to Ethionamide</td>
<td>High Dose INH</td>
</tr>
<tr>
<td>KatG</td>
<td>High level INH resistance and confers resistance to INH</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>InhA and KatG</td>
<td>Confers resistance to Ethionamide and High Dose INH</td>
<td>Neither INH nor Ethionamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May add PAS</td>
</tr>
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</table>
**TB SUSPECTS**

TB and DR-TB contacts, non-contact symptomatic individuals, re-treatment after relapse, failure and default

Collect one sputum specimen at the health facility under supervision

- **GXP positive**
  - Rifampicin susceptible
    - Treat as TB
      - Start on Regimen 1
      - Send one specimen for microscopy
    - Follow up with microscopy

- **GXP positive**
  - Rifampicin resistant
    - Treat as MDR-TB
      - Refer to MDR-TB Unit

- **GXP positive**
  - Rifampicin unsuccessful
    - Collect one specimen for microscopy
    - Culture & DST / LPA
    - Poor response to antibiotics
      - Clinically TB
      - TB on chest x-ray
    - Follow up with microscopy and culture

- **GXP negative**
  - HIV positive
    - Treat with antibiotics
    - LPA/ DST results
      - Resistant to R
        - Advise to return when symptoms recur
      - H/ R only
        - No further follow up
    - Good response
      - Advise to return when symptoms recur
    - Poor response
      - Consider other diagnosis
      - Refer for further investigation
  - HIV negative
    - Collect one specimen for a repeat GXP

- **GXP unsuccessful**
  - Collect one sputum specimen for microscopy
  - Culture & DST
  - For R and H
  - Treat with antibiotics and review after 5 days
  - Do chest x-ray
  - Poor response
    - Consider other diagnosis
    - Refer for further investigation
  - Good response
    - No further follow up
  - Advise to return when symptoms recur
  - Poor response
    - Consider other diagnosis
    - Refer for further investigation
  - Treat as MDR-TB
    - Refer to MDR-TB Unit
Principles of MDR-TB regimen (1)

- Include a minimum of four *effective* drugs

- Utilize parenteral therapy for a minimum of 6 months (ideally 4 months after culture conversion)

- Do not rely on drugs to which resistance is suspected or to which the patient has been previously exposed

- Include first-line drugs to which infecting strain is susceptible (but do not count them if patient has been previously exposed)
Principles of MDR-TB regimen (2)

When designing a regimen, think of the drugs in five

Group 1: Oral first line drugs

Group 2: Injectable agents

Group 3: Fluoroquinolones

Group 4: Oral second line agents with known efficacy against MTB

Group 5: Third-line agents active in vitro against MTB but limited data on in vivo activity
# Second Line TB Drug Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Group 1: First Line oral drugs</td>
<td>Ethambutol / Pyrazinamide/ INH</td>
</tr>
<tr>
<td>Group 2: Injectable Drugs</td>
<td>Kanamycin Amikacin Capreomycin</td>
</tr>
<tr>
<td>Group 3: Fluoroquinolones</td>
<td>Moxifloxacin Levofloxacin</td>
</tr>
<tr>
<td>Group 4: Oral Bacteriostatic Second Line Drugs</td>
<td>Ethionamide Terizidone Para-Aminosalicylic Acid (PAS) Cycloserine</td>
</tr>
<tr>
<td>Group 5 Re-inforcement drugs</td>
<td>Clofazamine Augmentin Clarithromycin Bedaqualine Linezolid High Dose INH</td>
</tr>
</tbody>
</table>
Principles of XDR-TB treatment

- Same as for MDR TB
- Even if patient is found to be resistant to fluoroquinolones, use a fluoroquinolone in the treatment (higher generation preferably) because of the presence of mixed strains, the ability of newer generation FQs to overcome resistance (depending on the mutation) and the risk of laboratory error
- Continue to use an injectable agent
- Use second- and third-line drugs as required to get up to at least four “active drugs”
‘Work up’ for patients with DR-TB

• Counselling - diagnosis, treatment, side effects and prognosis
• Sign consent for DR treatment – informed consent
• Baseline Audiometry (within 7 days of initiating DR-TB Rx)
• Bloods
  ▪ FBC, U&E + LFT, blood Sugar
  ▪ Thyroid Function Test
  ▪ Ca/PO4/Mg
  ▪ HIV test, CD4, VL, Hep BSag, Cryptococcal Ag (if applicable)
  ▪ Pregnancy Test, urine dipstix,
• Baseline CXR (and ECG)
• Multidisciplinary discussion
• Identify contacts (in ideal circumstances)
Monitoring Recovery

- Monthly monitoring includes:
  - **Clinically**
    - Weights, signs and symptoms, AE’s
  - **Bloods**
    - FBC, U+E, CMP, ALT/LFT
  - Sputa smear and cultures
- **Audiometry during injectable Phase**
- Serial X Rays (6/12/24 months)
- Thyroid Function Test 6 monthly
- **Initial Goal – culture conversion**
  - when 2 consecutive negative direct and cultures are achieved at least 30 days apart
Advice for Treatment Failures

**Unfortunate Reality**
- We have many treatment failures (> 300)
- They are being discharged home/into the community
- Some survive >5 years
- Expect more treatment failure with XDR-TB

**Plan for Failures**
- Complete adequate course of treatment (12-24 months)
- If failing treatment (9–12m), add what has not been used (Capreomycin, PAS, Klacid, Augmentin, Moxifloxacin, Clofazamine?)
- **Stop** all treatment **if** definite treatment failure (after 2yr)
- Palliative treatment, sanatorium or home-based care *(no current capacity, infection control concerns)*
MDR Treatment failures

• Problem
  ▪ What to do with treatment failures?

• Reason
  ▪ Anticipate increasing numbers of Treatment Failure
    • Lack of response to therapy
    • Poor adherence
      ~ Default as outpatients
    • Not enough drugs (XDRs)

• No easy options
  ▪ Reinforce adherence
    • Active exclusion from school / varsity/work till culture negative
  ▪ Consider Surgery (Lobectomy / Pneumonectomy)
  ▪ Look at Salvage regimens
    • Design salvage regimen (include meropenam /linozolid/Bedaquiline)
  ▪ Complete an adequate course
  ▪ National expert committee to discuss patients
    • Hospice /Palliative/ Terminal-End of Life care
Follow up after MDR-TB Rx

- Follow up for at least 2 years after completing a full course of treatment
- Review every 6 months and assess for:
  - Symptoms and signs of relapse
  - Smear and culture
  - CXR as needed for development of respiratory symptoms
## Common Side Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common Side Effect</th>
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<tbody>
<tr>
<td>Rifampicin</td>
<td>Hepatitis / Allergies/ Thrombocytopenia</td>
</tr>
<tr>
<td>INH</td>
<td>Hepatitis / CNS</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic Neuritis</td>
</tr>
<tr>
<td>PZA</td>
<td>Arthralgia (Raised Uric acid) / Hepatitis</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Ototoxicity / Nephrotoxicity</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Ototoxicity / Nephrotoxicity + Electrolyte disturbances</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Myalgia / Arthralgia / QT / CNS</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>GIT / Hypothyroidism</td>
</tr>
<tr>
<td>Terizidone</td>
<td>Fits / Psychoses / Suicidal / Depression / Neuropathy</td>
</tr>
<tr>
<td>Clofazamine</td>
<td>Skin discolouration / QT</td>
</tr>
<tr>
<td>PAS</td>
<td>GIT / Hypothyroidism</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>QT issues</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Bone Marrow suppression / Neuropathy / Optic Neuritis</td>
</tr>
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</table>
Managing DR-TB and HIV Co-infection

• Offer **ALL** patients HIV counselling and Testing
• **HAART for ALL** patients –not based on of CD4 or WHO stage

**ART Management:**

- 2013 DR-TB Guidelines suggest **AZT+3TC+EFV** (during Injectable phase)
- 2015 ART Guidelines suggest **ABC+3TC+EFV** for MDR TB patients
- **TDF+3TC+EFV (Atroiza)** can be started provided no contra-indications and renal monitoring is performed
- **ABC+3TC+EFV** in renal Impaired patients

• Monitoring of Patients as per 2015 ART guidelines
# Updated Drug-Resistant TB Treatment Outcome Definitions

(Effective for patients entered into the DR-TB Register from 01 January 2012)

<table>
<thead>
<tr>
<th>Cured</th>
<th>Treatment Completed</th>
<th>Treatment Defaulted</th>
<th>Treatment Failure</th>
<th>Transferred Out</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Culture converted</td>
<td>1. Culture converted</td>
<td>1. Treatment interrupted</td>
<td>1. In the final 12 months of treatment</td>
<td>1. Referred to another reporting &amp; recording unit</td>
</tr>
<tr>
<td>2. Received treatment for 18 months after culture conversion</td>
<td>2. Received treatment for 18 months after culture conversion</td>
<td>a) ≥2 consecutive months</td>
<td>a) ≥2 of 5 cultures are positive</td>
<td>2. Unknown treatment outcome</td>
</tr>
<tr>
<td>3. Clinically stable</td>
<td>3. Clinically stable</td>
<td>b) any reason</td>
<td>b) clinical condition deteriorating</td>
<td>Died</td>
</tr>
<tr>
<td>4. ≥3 consecutive negative TB cultures after injection phase (30 days apart)</td>
<td>4. &lt;3 consecutive negative TB cultures after injection phase (30 days apart)</td>
<td>c) without medical approval</td>
<td>3. At least 2 new drugs added because of poor clinical or x-ray response</td>
<td>1. Patient who dies for any reason during the course of treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Still on Treatment</th>
<th>Not Evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Still on treatment after 24 months</td>
<td>1. Patient recorded in the register and did not receive any of the above outcomes</td>
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</table>

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Treatment of DR TB – SA Plan

- Individualized Treatment – Rx according to DST
- Standardized Treatment – Treat according to best combination expected to cure patient

- SA has been practising Standardized treatment for MDR and XDR Treatment but things are changing
- Standard MDR – new MDR
  - 6 months injectable (minimum)
  - Kana (Amik)/Moxi /Ethio/Terizidone/PZA
  - 18 months continuation (minimum)
    - Moxi/Ethio/Terizidone /PZA
- XDR / Pre-XDR
  - With New drugs available we are moving to Individualized treatment in XDR/Pre-XDR and treatment failures
  - Choice of drugs is affected by previous exposure to 2nd line drugs
Bedaquiline Program KZN
**Initial BCAP in KZN**

- Started in 17/09/2013
- Screened 200 patients
- 68 patients commenced
  - Last on 6/2/2015
- 4 deaths
  - 1 Severe hypokalaemia (Lab/Power/Telecom constraints)
  - 3 possibly linked to Linezolid
    - 1 Anaemia / G/E / ? Embolus
    - 1 Severe Depression / apathy ffg. on Severe pancytopenia
    - 1 Severe Neutropaenia
- Much data outstanding – Capacity issues
New Drugs - Inclusion criteria (Prov)

- Lab confirmed RR (Genotypic or phenotypic)
  - XDR or Pre- XDR
  - MDR - Both inhA and KatG mutation
  - MDR with known intolerance or developed intolerance to 2nd line Rx (Renal / Ototoxicity)
  - Surgical candidate for pneumonectomy / Lobectomy

- Regardless of HIV status
- Inclusive of Extra pulmonary TB
- Must include 2 core drugs proven or thought to be effective or still sensitive
- Core Drugs from BDQ/LZD/Fluroquinolines/ Injectables

REQUIRES APPLICATION TO PROVINCIAL COMM
New Drug - National criteria

- > 3 months of XDR or Pre-XDR Rx prior to BDQ
- Less than 2 of the ffg core drugs sensitive / available
  - LZD - Don’t count if used before
  - BDQ – Don’t count if clofazimine used before
  - Quinolone – DST in last 3 months
  - Injectable – DST in last 3 months
- Does not have at least 1 other drug (sensitive or predicted sensitive)
- < 18 years
- Pregnant
- MDR Rx failures (without proven XDR)

REQUIRES APPLICATION TO NATIONAL COMM
• Levofloxacin preferable
  - Unless proven Moxifloxacin sensitive
  - If Moxifloxacin used – weekly ECGs for 1/12 than monthly

• Drug interactions
  - Neuroleptics
  - Tricyclic Antidepressants
  - Class 1a or Class III antiarrhythmic drugs

• Baseline & monthly ECGs
  - Weekly for 1st month if clofazimine/moxifloxacin used

• ARV’s
  - Switch from EFV
  - If not suppressed may require 2 drug switch

• Linezolid for 12 months if possible
HIV infected patients

- NVP and 2 appropriate NRTIs
  - if the CD4+ is< 250 in women and 350 in men
- LPV/r-regimen with 2 appropriate NRTI for
  - Patients that require second line therapy or
  - have CD4+ is greater than 250 in women and 350 in men
- While Rilpivirine and raltegravir can be considered
  - if on tender
- Interactions
  - EFV reduces BDQ
- Viral load before BDQ
  - If suppressed VL and a nadir CD4+ less than 250 in women and 350 in men, change to NVP.
  - If not full viral suppression or a higher nadir, then consider LPV/r
MDR-TB is defined as TB disease where there is resistance to:

A. Rifampicin

B. At least Rifampicin and Isoniazid

C. Isoniazid and Rifampicin and Moxifloxacin

D. Isoniazid and Rifampicin and Kanamycin

E. INH
Patients with MDR-TB and HIV co-infection should be commenced on ARVs with a CD4 count of:

A. $\leq 200 \text{ cells/mm}^3$
B. $\leq 350 \text{ cells/mm}^3$
C. 500 cells/mm$^3$
D. Any CD4 count
Case study

- A 41 year old female was referred to the DR-TB facility in November 2012 with a **positive Xpert MTB/RIF result** showing Rifampicin resistance.
- She complained of cough, loss of weight and night sweats.
- On examination, she was ambulant, wasted, but not distressed; with bilateral basal crackles.
- CXR showed bilateral disease
- She was cured of Drug Sensitive TB in 2001
- In Feb 2012 she was diagnosed with HIV and started on Atroiza. Her baseline CD4 was 85c/ml
Her Gene Xpert Result is below

Specimen received: Sputum

Tests requested: GeneXpert @

  @ Test referred to another laboratory

Real time PCR for M. tuberculosis (GeneXpert):

- PCR result: Mycobacterium tuberculosis complex detected
- Rifampicin: Resistant
What MDR-TB treatment would she be started on while awaiting Culture and DST?

A. Amikacin, Terizidone, Ethionamide, Moxifloxacin, Pyrazinamide and Isoniazid

B. Kanamycin, Terizidone, Ethionamide, Moxifloxacin, Pyrazinamide and Isoniazid

C. Streptomycin, Terizidone, Ethionamide, Moxifloxacin, Pyrazinamide and Isoniazid
Her LPA result comes back and shows an InhA mutation. What drug SHOULD NOT be used because of resistance?

A. Moxifloxacin
B. Rifampicin
C. Ethionamide
D. High Dose INH
E. Terizidone
Case continued

• She develops seizures after starting the MDR TB treatment. Which MDR TB drug is likely the cause?

A. Terizidone
B. PZA
C. Ethionamide
D. Kanamycin
Case continued

Which of the following drugs DO NOT commonly cause renal impairment or hearing loss?

A. Kanamycin
B. Moxifloxacin
C. Amikacin
D. Streptomycin
What should be monitored carefully in a patient on Bedaquiline and Clofazamine

A. Hearing  
B. Liver function  
C. ECG - QTC interval  
D. Drug levels
What side effects can occur with Linezolid?

A. Peripheral Neuropathy
B. Optic Neuritis
C. Bone Marrow Suppression
D. All of the Above
Acknowledgements

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