Shortened DR- TB Regimens & Regimens for XDR TB

Iqbal Master
Clinical Manager
KDHC
57% of TB patients are HIV +

6th highest incidence of TB cases

287,224 New & Relapse TB cases

64% DR-TB cases started on treatment

5th highest incidence of DR-TB cases

48% MDR-TB Treatment Success

2015 Data

TB in South Africa

Slide Courtesy of Johns Hopkins School of Nursing The Reach Initiative
DR-TB Treatment Initiation

DR-TB Initiation on Treatment in South Africa, 2009-2014

WHO South Africa: Towards Universal Health Coverage, 2016 Report

Slide Courtesy of Johns Hopkins School of Nursing The Reach Initiative
DR-TB Diagnosis and Treatment Gap

Gap Between MDR-TB Diagnosis & Treatment in South Africa, 2009-2014

WHO South Africa: Towards Universal Health Coverage, 2016 Report

Slide Courtesy of Johns Hopkins School of Nursing The Reach Initiative
**EVOLUTION OF SA DR-TB TREATMENT**

- **Before 1996** - Individualized MDR Rx
- **1997-2005** - Standardized MDR Rx (MRC Guidelines)
- **2006 - 2013** - DOH guidelines
  - Standardized treatment for MDR & XDR
- **2014 onwards**
  - MDR TB - Standard MDR Treatment
    - 6 months injectable (minimum)
      - Kana or Amik / Moxi / Ethio / Terizidone / PZA
    - 18 months continuation (minimum)
      - Moxi / Ethio / Terizidone / PZA
  - Pre-XDR / XDR - Individualized regimen
    - Regimens structured around Bedaquiline +/- Linezolid
- **2017 - The Current and Future**
  - Shorter Regimen for most MDRs based on new WHO policy
  - Pre-XDRs / XDRS / Double INH Mutations / Rx failures - Individualized Regimen
<table>
<thead>
<tr>
<th>GROUP A</th>
<th>Fluoroquinolones</th>
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<tbody>
<tr>
<td></td>
<td>Levofloxacin</td>
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<td>Moxifloxacin</td>
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<td>Gatifloxacin</td>
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<thead>
<tr>
<th>GROUP B</th>
<th>Second-line injectable agents</th>
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<tr>
<td></td>
<td>Amikacin</td>
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<td></td>
<td>Capreomycin</td>
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<td></td>
<td>Kanamycin</td>
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<td></td>
<td>(Streptomycin)</td>
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<table>
<thead>
<tr>
<th>GROUP C</th>
<th>Other Core Second-line Agents</th>
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<tbody>
<tr>
<td></td>
<td>Ethionamide / Prothionamide</td>
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<td></td>
<td>Cycloserine / Terizidone</td>
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<td></td>
<td>Linezolid</td>
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<td></td>
<td>Clofazimine</td>
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</table>

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<thead>
<tr>
<th>GROUP D</th>
<th>Add-on agents (not core MDR-TB regimen components)</th>
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<tbody>
<tr>
<td>D1</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td>High-dose isoniazid</td>
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<tr>
<td>D2</td>
<td>Bedaquiline</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
</tr>
<tr>
<td>D3</td>
<td>p-aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Imipenem-Cilastatin</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin-Clavulanate (Thioacetazone)</td>
</tr>
</tbody>
</table>
NEW SHORTENED REGIMEN IMPLEMENTED IN RSA

November 2016
January 2017 (Some Provinces)
5 June 2017 (KZN)
11 Sep (WP)
The WHO updated treatment guidelines on DR-TB in May 2016 to include shorter MDR-TB regimen under specific criteria.

South Africa will adopt the WHO Short MDR-TB Regimen as the Standard Short (9-12 Months) Regimen to replace the existing regimen based on an inclusion/exclusion criteria on 1 April 2017.

Any MDR-TB patient who is not eligible for the Modified Short Regimen should continue with the Standard Extended (18-20 months) Regimen.

Slide Courtesy of Johns Hopkins School of Nursing The Reach Initiative
Summary of MDR-TB Regimens in SA

**Standard Short Regimen** – All new patients
- 4-6 \( Km + Mfx + Cfz + Eto + Z + H + E \) / 5 \( Mfx + Cfz + Z + E \)

**Short Bedaquiline Regimen** – Switched If A/Es
- 4-6 \( Bbq + Lfx + Cfz + Eto + Z + H + E \) / 5 \( Lfx + Cfz + Z + E \)

**Standard Extended Regimen** – Severe X/Pulm TB
- 6-8 \( Km + Mfx + Cfz + Eto + Z + H + E \) / 12-14 \( Mfx + Cfz + Z + E \)

**Individualised Extended Regimen** – 18 -24 mths
- Xdr /Pre-XDR/Both mutations/ Failures

Pyridoxine Supplementation
- All regimes including Cycloserine, Terizidone or high dose INH should add pyridoxine/B6
Rifampicin Resistance Algorithm for Patient Management

GeneXpert + Rif Resistance

Baseline Visit Evaluations
Submit specimen for DR-TB Reflex (FL-LPA, SL-LPA, Smear/Culture, and pDST for preXDR & XDR), *Labs, CXR, Audio

Start Short Course TB Treatment
4-6 Km + Mfx + Cfv + Eto + Z + H\textsuperscript{h} + E / 5 Mfx + Cfv + Z + E
Excludes complicated EPTB (Bone, Joints, Meningitis) or prior SL-resistance to aminoglycosides or fluoroquinolones

Monitor monthly smear/culture
If smear negative at month 4, STOP the intensive phase
See Determining Duration Table

Review DR-TB Reflex (FL-LPA & SL-LPA) results after 7-14 days
If no valid result, continue treatment and follow-up LPA results at Day 28
LPA results are generally available in two weeks for Smear + patients; Smear - patients take longer for LPA results

INH Sensitive
NO katG or inhA
Continue Short Course
If patient has prior SL treatment exposure, contact the lab for pDST

Single mutation
katG OR inhA
katG only
Drop H\textsuperscript{h}
InhA only
Drop Eto
Continue (Adjusted) Short Course
If patient has prior SL treatment exposure, contact the lab for pDST

Double mutation
Both katG & inhA

Injectable Resistance
Immediately Refer to Centre with Access to Newer Drugs
Start new regimen
Treat for 18-20 months

Fluoroquinolone +/- Injectable Resistance

Ototoxicity or Renal Impairment (CrCl below 60mL/min)

NO
YES

Continue Short Course for 9-12 months
Immediately Refer to Centre with Access to Newer Drugs
Start new regimen

Patient will require regimen selection and initiation under the supervision of a Medical Officer

Legend
BDQ Bedaquiline
Ca Calcium
Cfv Clofazimine
pDST Phenotypic Drug Sensitivity Test
EPTB Extrapulmonary TB
Eto Ethionamide
FBC Full Blood Count
FL-LPA First-Line LPA
H\textsuperscript{h} Isoniazid (High Dose)
Km Kanamycin
Mg Magnesium
Mfx Moxifloxacin
SL-LPA Second-Line LPA
TSH Thyroid Stimulating Hormone
U&E Urea/Electrolytes
Z Pyrazinamide

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WHO QUALIFIES FOR WHICH REGIMEN

- MDR patients will get a shortened regimen (9-12 mths)
  - New MDRS
  - Retreatment MDRs (Previously cured / Review after Reflex test)
  - Paediatrics - (who can take the 100mg clofazimine +/- 20kg)
- All patients will have a 2\textsuperscript{nd} line LPA (reflex test done)
- Severe forms of extrapulmonary TB will get a longer regimen

- The following will qualify for new drugs (Bedquiline)
  - Long Regimens
    - XDR & Pre-XDR
    - Both INH mutations -long
    - Treatment failures -
  - Short regimen
    - MDR patients with A/E
    - Pregnant ladies
<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 but usually confers resistance to Ethionamide</td>
<td>High Dose INH / Ethionamide</td>
</tr>
<tr>
<td>KatG</td>
<td>High level INH resistance confers resistance to INH, but Ethionamide should be sensitive</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>Gyr A &amp; GyrB</td>
<td>Ofloxacin resistance</td>
<td></td>
</tr>
<tr>
<td>RRS &amp; EIS</td>
<td>Injectable resistance</td>
<td></td>
</tr>
</tbody>
</table>
Standard SHORT Regimen

**Intensive Phase (4-6 months)**

\[ \text{Km} + \text{Mfx} + \text{Cfz} + \text{Eto} + \text{Z} + \text{H}^h + \text{E} \]

**Continuation Phase (5 months)**

\[ \text{Mfx} + \text{Cfz} + \text{Z} + \text{E} \]

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Weight</th>
<th>33-50kg</th>
<th>50kg to 70kg</th>
<th>&gt; 70</th>
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<tr>
<td>Kanamycin</td>
<td>15mg/kg (max 1g)</td>
<td>400mg</td>
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<tr>
<td>Moxifloxacin</td>
<td>400mg</td>
<td>400mg</td>
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<td>Ethionamide</td>
<td>250mg</td>
<td>500mg</td>
<td>750mg</td>
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<tr>
<td>Isoniazide (HD)</td>
<td>600mg</td>
<td>600mg</td>
<td>900mg</td>
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<tr>
<td>Clofazimine</td>
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<td>Ethambutol</td>
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<td>800mg</td>
<td>1200mg</td>
<td>1600mg</td>
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<tr>
<td>Pyrazinamide</td>
<td>1000mg</td>
<td>1500mg</td>
<td>1750mg</td>
<td>2000mg</td>
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<tr>
<td>Bedaquiline</td>
<td>400mg dailty 2 weeks – thereafter 200 mg 3 times a week</td>
<td>400mg</td>
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<tr>
<td>Levofloxacin</td>
<td>750mg</td>
<td>750mg</td>
<td>1000mg</td>
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</tbody>
</table>

Slide Courtesy of Johns Hopkins School of Nursing The Reach Initiative
## Monitoring and Determining Duration of Intensive Phase in MDR-TB Treatment

**At baseline send DR-TB Reflex** - If LPA results have not returned at 1 month, submit a repeat sample for DR-TB Reflex.

**Smear determines duration, culture determines treatment outcome**

- Monthly cultures are to be requested in addition to smear microscopy.
- If smear negative at 4 months, STOP the intensive phase.
- If smear **positive** at 4 months, REFER and CONTINUE the intensive phase, send repeat DR-TB Reflex and request pDST.
- If smear **positive** at 6 months, SWITCH to a new (and extended) regimen.

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<thead>
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<th>Month</th>
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**If smear is still + in Month 4, refer the patient to MDR-TB specialist and send repeat DR-TB Reflex and request phenotypic DST from the lab.**

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<tr>
<th>Month</th>
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<tbody>
<tr>
<td>Smear</td>
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<td>Sm (−)</td>
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</tbody>
</table>

**Treatment failure** REFER and SWITCH to new regimen.
CURRENT AND FUTURE DEFINITIONS

Definitions of a cure - (long regimen)
- MDR patient (Cat IV), received **18 months** Rx, culture converted, clinically stable and has 3 or more consecutive negative cultures after injectable phase

Definitions of a cure - (shortened Regimen)
- MDR-TB patient (CAT IV) who has culture converted, received 9 months (or more), clinically stable and has 3 or more consecutive negative cultures after the injectable phase.
FOLLOW-UP AFTER CURE FOR SHORT REGIMEN

- Patients with DR-TB must be followed up 6 monthly for at least 2 years after cure/completion
- Assess for signs and symptoms of relapse
- Conduct smear and culture every six months
Monitor Bloods

- Repeat U & E for patients on injectables
  - (monthly )
- Monitor Ca/PO4/Mg - on injectables/ BDQ
- TFTs - PAS + Ethionamide

Serial Audios - on injectables
  - Monthly if possible

Side Effect monitoring program should be in place.

Response to therapy is monitored by
  - monthly cultures & weights
  - Serial X Rays - where available
CHALLENGES – OF THE SHORT REGIMEN

- Higher doses of INH advocated are resulting in an increase in
  - DILI
  - Peripheral neuropathy
  - Possible increase in Psycoses

- Availability of Clofazimine has impacted on roll out

- Clofazimine (section 21) - requires patient consent
  - Some patients have refused clofazimine
  - Additional paper work and import permits
  - Nurse Driven programs have difficulty accessing clofazimine

- SA program has started with a lower dose of Moxifloxacin (400mg) - uncertain impact
  - Higher doses may be required with additional ECG monitoring

- Many areas could not implement 6-7 days a week Kanamycin

- Many of Reflex Tests not available - causing uncertainty on which regimen to use (~ 40%)
  - Failure to send it
  - Inconclusive results
POSSIBLE CHANGES BEING CONSIDERED

- Using hINH despite KAT G mutation
  - As done in Bangladesh Regimen
- Using a lower dosage of INH
  - 900mg may not be necessary
- Using a higher dose of Moxifloxacin
  - As done in Bangladesh Regimen (600mg)
  - ? 800mg +/- ECG monitoring
- Intermittent Kanamycin at higher dosage
  - ? 25mg 3x a week
- ? Treating all Retreatment MDRs with Individualized regimen
- No of the above confirmed - National committee to make final decisions
Discussion from National committee

- Reflex test not always available
- If no reflex test available
  - Manage patients clinically
  - Assess response to therapy
    - Smear
    - Culture
    - Weight Gain
    - Xray
  - 9 - 12 months should be enough
- If clinically unwell and sputum positive is probably failing - and manage as such
KZN Team

BEDAQUILINE
PROGRAM
KZN
Bedaquiline -
- Long half life (5 months)
- 400 mg (daily) for 2 weeks
- 200 mg (3 times a week) for 22 weeks
- Background regimen (BR) of 2nd line drugs (XDR/Pre-XDR) to be continued (duration of course)
- Part of National TB program 2013
- Approval at Provincial or National Committee
CRITERIA FOR PROVINCIAL APPROVAL

- XDR or Pre-XDR
- MDR TB (including RR TB)
  - MDR - Both inhA and KatG mutation
  - MDR with known intolerance or developed intolerance to 2\textsuperscript{nd} line Rx Drug Toxicities
- Regardless of HIV status (or CD 4 count)
- Inclusive of extrapulmonary TB
CRITERIA FOR NATIONAL APPROVAL

- Pre-XDR or XDR - with fewer than 2 core drugs thought to be effective, sensitive and available
  - Quinolones / Injectables
  - Linezolid / Bedaquiline ( > 3 mths Clofazimine)

- Age < 18 years
  - Pre-XDR, XDRs, Treatment Failure, Drug toxicities

- Pregnancy

- MDR Rx failures (without proven XDR/Pre-XDRs)
Levofloxacin preferred to moxifloxacin (QTC risk)

Monitoring
- ECG - 2 weekly for 1st month thereafter monthly
- Blood monitoring monthly (depending on drugs used)

2 considerations - QT prolongation / Enzyme Induction

ARV switch often required
- Current Primary regimen is TDF/3TC/EFV
- Need to Switch EFV (Decreases BDQ levels)
- Often switched - EFV to NVP or to Alluvia (Lopinavir/Ritonovir) /
  - Raltegravir / Ralpivarine also acceptable
  - If not suppressed may require 2 drug switch

BDQ is used for 6 months

If Linezolid used - for up to 12 months (if tolerated)
<table>
<thead>
<tr>
<th><strong>KZN Bedaquiline Program Data</strong></th>
<th><strong>3/9/2017</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients application</td>
<td>2554</td>
</tr>
<tr>
<td>Patients approved</td>
<td>2420</td>
</tr>
<tr>
<td><strong>Patients actually commenced</strong></td>
<td>1977</td>
</tr>
<tr>
<td>Started at KDHC</td>
<td>1670</td>
</tr>
<tr>
<td>Doris Goodwin</td>
<td>151</td>
</tr>
<tr>
<td>Murchison</td>
<td>51</td>
</tr>
<tr>
<td>Manguzi</td>
<td>21</td>
</tr>
<tr>
<td>Estcourt</td>
<td>13</td>
</tr>
<tr>
<td>Deaths on BDQ (Total Deaths - from applications)</td>
<td>134 (211)</td>
</tr>
</tbody>
</table>
KDHC has filled up with BDQ patients
- Difficulty tracking a Fast tracked program
- Pharmacovigilance is weak and needs to be strengthened
- BDQ is being decentralized and needs to continue

We have made great strides in rapidly rolling out a new drug program in a short period
- Need to expand access
- Need to analyze data, and outcomes to judge the impact
- Need to review and strengthen the program.
- Need to look at the morbidity and mortality & A/E
CLINICAL CHALLENGES

- Where XDR TB/Pre-XDr TB ruled out BDQ is used alone to substitute for KANA
  - Some patients do not respond well to BDQ alone
  - BDQ extension is being used in some - but not for a failing patient
- We are getting treatment failure / defaulters to BDQ/LZD based regimen - way forward is not always clear.
- We have had a fair no of deaths on BDQ & many are very ill - but these deaths need analysis
- With Long half life - it becomes difficult to manage defaulters
- Adverse events attributed to especially LZD are difficult to manage as outpatients unless you are vigilant and have a robust monitoring system
HOW TO APPROACH BDQ/LZD FAILURES

- Do a special sensitivity test
  - Specimen sent to NICD (National Lab)
    - Sensitivity tests for all standard drugs
      - Including Linezolid / Capreomycin /EMB /Rifabutin
    - Special tests sensitivity to BDQ and Clofazimine
- Consider for Surgery
- Look at salvage regimen based on above NICD test
- Optimize HAART
- Enhanced adherence counselling & commitment
- Consideration for the use of Carbepenams - IV
- Application for Compassionate usage for Delaminind (with BDQ) - Long process
- Non BDQ/LZD failures - can be considered for the NIX study
WAY FORWARD FOR BDQ PROGRAM

- Expand Bedaquiline access
  - Doris Goodwin
  - Murchison
  - Manguzi
  - Estcourt
  - St Margaret's
  - Catherine Booth
  - Greytown
  - Charles James

- Sites starting shortly
  - Madadeni
  - Don Mackenzie

- Requirements to expand
  - Knowledge, understanding & training on MDR & BDQ issues
  - ECG machine
  - Adequate recording & reporting
  - Demonstrateable Competence in managing MDRs
CLOFAZIMINE(CFZ) (50MG/100MG)

- Binds preferentially to mycobacterial DNA and inhibits mycobacterial replication and growth.
- Long half life - months
- Side effects:
  - ichthyosis, and dry skin
  - Darkening / discolouration of skin
  - anorexia
  - abdominal pain.
- Use with caution in Liver DX
- Currently a section 21 Drug - requires patient consent
- Quantification and availability has impacted on roll out
LINEZOLID (ZYVOXID)

- Linezolid is an oxazolidinone
- Is a protein synthesis inhibitor
  - it stops growth of bacteria
  - Proven Activity against MTB
- Long term usage is associated with serious A/E
  - bone marrow suppression
    - Thrombocytopenia / Anaemia / Neutropenia
  - Severe peripheral neuropathy
  - Optic neuritis - reversible if picked up early
  - Lactic acidosis - ? due to mitochondrial toxicity
- Linezolid - no effect on the QT interval
**LINEZOLID IN SA NEW DRUG GUIDELINES**

- **Avoid if**
  - severe anaemia (Hb< 7) - consider transfusion
  - severe peripheral neuropathy

- **Dosage**: Currently Start at 600mg daily. ( > 30kg)

- **Used for 12 months in current program**

- **Stop if toxicity**, life threatening or worsens.

- **If bone marrow suppression** -
  - Stop Linezolid - wait for a response and restart at a reduced dose ( 300mg) - if needed
  - May need transfusion
DELAMINID

- Novel TB Drug related to Metronidazole (Otsuka)
- Bound by albumin
- Safety
  - Established in children
  - No ARV switch required
  - ECG monitoring required (QT issues)
  - Possible Low barrier for resistance than BDQ
- Available
  - via a Compassionate usage program
  - DCAP program
Delaminid can be accessed by 2 pathways

- **DCAP - SA program** - Where DLM preferred above BDQ - slow uptake
  - Virally suppressed and don’t want ARV change
  - Previous Clofaz exposure > 3 mths
  - Where BDQ is contraindicated
    - QTC 450 - 500
  - 12 - 18 years of age
  - > 35 kgs
  - Anaemia - to replace LZD (But not with BDQ)
  - Pre-XDR
  - Diabetes Mellitus / other with expected poor outcomes

**Compassionate usage**

- Treatment failures
  - Using BDQ with Delaminid
- Outside Criteria for DCAP
  - Less than 35 Kg
  - Children < 12 years
  - XDR s

**KDHC is approved for DCAP**

- Difficulty finding suitable cases ???

Awaiting National meeting and discussion
35 year old / RVD Positive / weight 52kg
On ARVS TDF/3TC/EFV since 2014
Virally suppressed (LTDL) / CD4 - 150
No Past PTB
Now found to have Gene Xpert Positive and RIF resistant on 25/08/2017
QUESTION 1: WHAT TREATMENT WOULD YOU START HIM ON

1. Short Bedaquiline Regimen (9-12mths)

2. Standard Extended Regimen (18-22mth)

3. Standard Short Regimen (9-12 mths)

4. Individualised Extended Regimen (18-24 mths)

5. Old Regimen - (18-24mths)
Patient becomes smear neg at month 2
Appears to be doing well responding to treatment
1st line LPA comes back with an INH A Mutation
Has gained 1kg
1. 6 months injectables and stop INH & add PAS
2. 4 months injectables and stop Ethionamide
3. 8 months injectables and stop Ethionamide
4. 6 months injectables and no change
5. 4 months injectables and start Bedaquiline
Patient at month 3 - doing well but found to have moderate ototoxicity
- Chest xray cleared further
- Has gained 3kg
QUESTION 3: WHAT FURTHER TREATMENT CHANGES WOULD YOU MAKE, IF ANY?

1. Has had enough injectables (3 months) - would stop the injectable continue the short regimen

2. Hearing loss is not serious. The patient is responding well. Change the injections to 3 times a week and continue the short regimen

3. Would stop the injectable and substitute with 2 other drugs like Terizidone and PAS

4. Hearing loss is significant. Would stop the injectable and apply for Bedaquiline but would still continue the short course

5. Patient is doing well would continue the regimen being used
Reflex test was inconclusive on the smear

The reflex test was done from the cultured isolate & showed
- Rifampacin sensitive but resistant to INH
- 2nd line LPA showed Fluroquinolone resistance sensitive to the injectables

Chest xray has cleared even further

Has gained 2 kg
1. Patient is doing well no change in regimen. (9-12 mths)

2. Patient is doing well. He is on Bedaquiline already so no change in regimen - treat for 18-24 months

3. This is a PRe-XDR. Change to individualized regimen (18-24 mths) - add Bedaquiline and PAS

4. Patient is Pre-XDR and still sensitive to injections. Restart the injectables and treat for (18-22 mths)

5. Rif is sensitive - stop MDR treatment and start Rifafour
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• Staff from all the MDR units - for their hard work

Thanks to the organisers of the conference for inviting me

• We all need to understand the short regimen
• Whether we like it or not we need to support it
• MDR care needs to be unpacked to PHC & CHC
• KZN is lagging behind all the other provinces in decentalization

Thank you To All Health Care workers working in HIV and TB