DR-TB Treatment

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Strategy shift

Individualized Practitioner Approach (Before 1998)  WHO  Community Based Programmatic Approach (After 1998)

International Partners
Drugs in TB Management

WHO 2008

1st line drugs: (HR)ZE
Most efficacious and best tolerated

Injectable: S, Km, Cm, Am
Bactericidal

Fluoro quinolone: Mfx, Lfx, Ofx
Highly bactericidal

Less efficacious and poorly tolerated

Other 2nd line drugs: Cs, PAS, Pto/Eto

Weak anti-TB action

Unclear drugs: Cla, CoA, Clofa, Linz
Imipenem, thia, high dose H
MDR-TB
How to Treat?

Guiding Principles

- Use at least 4 drugs highly likely to be effective (5-7 if doubtful)
- Do not use drugs for which resistance crosses over
- Eliminate drugs that are not safe in the patient
- Include drugs from Groups 1-5 in a hierarchical order based on potency
- Be prepared to prevent, monitor and manage adverse effects for each of the drugs selected

WHO/HTM/TB/2006.361
MDR/XDR-TB
How to Select Drugs?

- DST shows susceptibility
- No previous history of treatment failure with the drug
- No known close contact with resistance to drug
- DRS survey indicate rare resistance to drug
- At least one injectable and one fluoro quinolone
# Cross-Resistance Between Anti-tuberculosis Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cross Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>High level cross-resistance with other rifamycins</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>Variable cross-resistance; some newer generation drugs remain susceptible when lower-generation</td>
</tr>
<tr>
<td>Aminoglycosides and polypeptides</td>
<td>drugs are resistant</td>
</tr>
<tr>
<td>Aminoglycosides and polypeptides</td>
<td>Amikacin and kanamycin have high cross-resistance</td>
</tr>
<tr>
<td></td>
<td>Capreomycin and viomycin have high cross-resistance</td>
</tr>
<tr>
<td></td>
<td>Variable cross-resistance between other drugs</td>
</tr>
<tr>
<td>Protionamide and ethionamide</td>
<td>High level cross-resistance; cross resistance to INH if inhA mutation present</td>
</tr>
<tr>
<td>Thioacetazone</td>
<td>Variable and low cross-resistance to isoniazid, ethionamide and PAS</td>
</tr>
</tbody>
</table>
Regimen Design
Basic Principles

- Drugs given at least 6 days/week, preferably OD schedule
- Dosage linked to body weight with preference for higher dosage of the range
- Injectable for minimum 6 months
- Treatment for minimum 18 mths beyond sputum culture conversion
DOT throughout treatment

PZ can be used throughout treatment as inflammation leads to acidic environment wherein it acts effectively

Early detection and prompt treatment are important for successful outcomes
MDR-TB
How to Treat?

Treatment options

• Empirical treatment strategy
• ITR
• STR
Treatment Strategy
STR Vs ITR

**Advantage**
- Cost of regimen moderate
- DST of all drugs is not required
- Technical capacity of physician may not be high
- Easier applicability or larger scale
- Simpler operational aspects of implementation
- Simpler drug ordering
- Easier training
- Less likelihood of mismanagement in the periphery
STR Vs ITR

Disadvantage

• Not as effective as ITR in all situations
• Possibility of amplification of resistance
• Drug susceptibility pattern within community needs to be well documented – DRS essential
• Organism may be resistant to some of the drugs of the regimen with avoidable increase of cost and toxicity
MDR Treatment Strategies based on Lab. Method to Confirm MDR

**Conventional methods**

- While awaiting DST results for H and R
- Empirical treatment with MDR regimen
  - Continue standard MDR regimen or
  - Change to individualized MDR regimen (once DST for 2nd-line drugs is available)

**Rapid methods**

- Once MDR is confirmed in 1-2 days
  - Standard MDR regimen OR
  - Individualized MDR regimen (once susceptibility testing for 2nd-line drugs is available)
Treatment Strategy
Role of Surgery

- Adjunct to chemotherapy
- Not indicated in extensive bilateral disease
- 2 months ATT prior to surgical resection
- SLD to continue for at least 24 months
- Trained thoracic surgeon with good post operative management essential
National DOTS Plus
How to Treat MDR?

National Policy - S.T.R.

- I.P. : - 6 to 9 months
  - Kana, Oflox, Ethio, Cyclo, Z, E
  - Shift from IP to CP based on at least 2 consecutive negative sputum cultures

- C.P. : - 18 months after 1\textsuperscript{st} culture negative
  - Ethio, cyclo, oflox, E ( +/- Z)

- PAS substitutes, if one cidal or two static drugs not tolerated.
National DOTS Plus
How to Monitor?

- Sputum D/S and Culture
  - IP monthly
  - CP every 2-3 mths.
- X-ray every 6 month
- S. Creatinine every month for 1\textsuperscript{st} three months and every quarter till injections are taken.
- LFT, Blood sugar and Thyroid Function Test at initiation and as and when required
- Offer HIV testing
- Pregnancy test for females in reproductive age group
Treatment of XDR-TB

- Use an injectable agent and consider an extended duration of therapy
- Use a higher generation FQN such as moxifloxacin
- Consider high-dose INH if low-level resistance is documented
- Use Group 4 and 5 drugs
- Consider surgical resection
- Treat underlying HIV infection
- Provide comprehensive monitoring and treatment of side-effects

WHO. Guidelines for the programmatic management of drug-resistant TB, 2008
## MDR Tuberculosis
### Predictors of Success and Failure

<table>
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<th>Success</th>
<th>Failure</th>
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<tr>
<td>• Use of pyrazinamide and/or ethambutol, if susceptible</td>
<td>• Previous therapy</td>
</tr>
<tr>
<td>• Use of a fluoroquinolone</td>
<td>• Number of drugs resistant</td>
</tr>
<tr>
<td>• Use of &gt; 5 drugs</td>
<td>• Resistance to FQN</td>
</tr>
<tr>
<td>• Sputum conversion by 2 months</td>
<td>• Resistance to capreomycin</td>
</tr>
<tr>
<td>• Surgical resection</td>
<td>• Presence of cavitation</td>
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<tr>
<td></td>
<td>• Low BMI</td>
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<tr>
<td></td>
<td>• HIV infection</td>
</tr>
<tr>
<td></td>
<td>• Poor adherence</td>
</tr>
<tr>
<td></td>
<td>• Positive cultures at 2-3 mos</td>
</tr>
<tr>
<td></td>
<td>• XDR-TB</td>
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## Recommended Strategies for Different Programmatic Situations

<table>
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<tr>
<th>Patient Group</th>
<th>Background</th>
<th>DST Data</th>
<th>Strategy</th>
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</table>
| Cat I Failure | Low % have MDR-TB 2\textsuperscript{nd} line DR is rare | • Perform DST to H and R at minimum in all patients  
• Start Cat II treatment  
• Adjust regimen to Cat IV if DST reveals DR-TB |
| High % have MDR-TB 2\textsuperscript{nd} line DR is rare | • Perform DST to H and R at minimum in all patients  
• Start Cat IV treatment  
• Adjust regimen according to DST |
| High % have MDR-TB 2\textsuperscript{nd} line DR is common | • Perform DST to H, R, IA, FQ before treatment starts  
• Start Cat IV treatment  
• Adjust regimen according to DST |

WHO. Guidelines for the programmatic management of drug-resistant TB, 2008
# Recommended Strategies for Different Programmatic Situations

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<td>Cat II Failure</td>
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<td>• Perform DST to H and R at minimum in all patients</td>
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<td>2nd line DR is rare</td>
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<td>• Start Cat IV treatment</td>
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<td></td>
<td></td>
<td>• Adjust regimen according to DST</td>
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<tr>
<td>Relapse or return after default</td>
<td>Low to moderate rate of MDR-TB</td>
<td>• Perform DST to H and R at minimum in all patients</td>
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<td>• Start Cat II treatment</td>
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</table>
| Documented MDR-TB   | Documented, or almost certain, susceptibility to FQ and IA         |                                                           | • Start Cat IV treatment  
• Adjust regimen according to DST                                         |
|                     | Documented, or almost certain, susceptibility to FQ, resistance to IA |                                                           | • Start Cat IV treatment  
• Use an IA with documented susceptibility  
• If resistant to all, try one that resistance is rare |
|                     | Documented, or almost certain, resistance to FQ, susceptibility to IA |                                                           | • Start Cat IV treatment  
• Use a later generation FQ                                                   |
|                     | Documented, or almost certain, resistance to FQ and IA             |                                                           | • Start Cat IV treatment for XDR-TB                                         |

WHO. Guidelines for the programmatic management of drug-resistant TB, 2008
CONCLUSION

- Designing treatment regimens for MDR-TB are challenging
- STRs are preferred over ITRs under NTPs in resource limited settings
- Different options for STR are available linked to the DRS pattern in the country
- Decision on the regimen is linked to the resources, availability of quality assured DST, ADRs, drug availability
THANK YOU

MDR-TB

DOTS / PMDT